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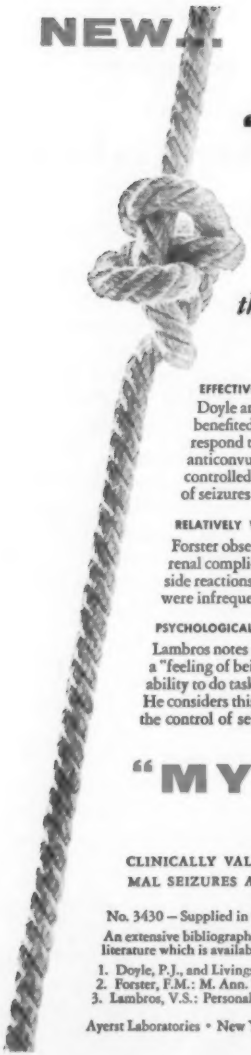

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1. Doyle, P.J., and Livingston, S.: J. Pediat. *43*:413 (Oct.) 1953.
2. Forster, F.M.: M. Ann. District of Columbia *23*:137 (Mar.) 1954.
3. Lambros, V.S.: Personal Communication.

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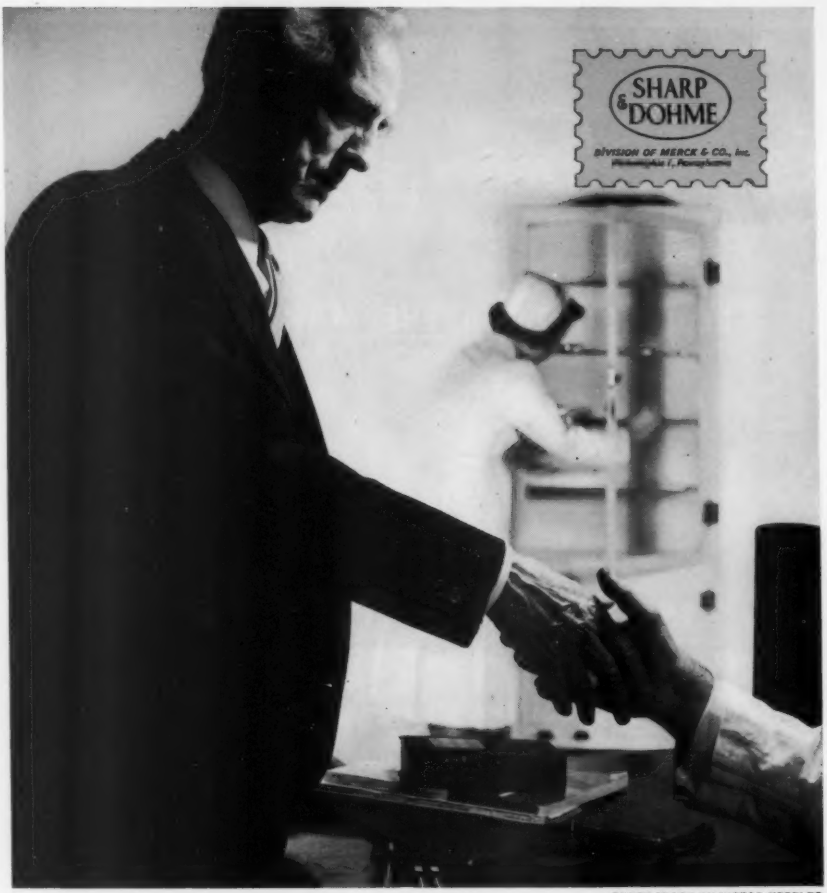

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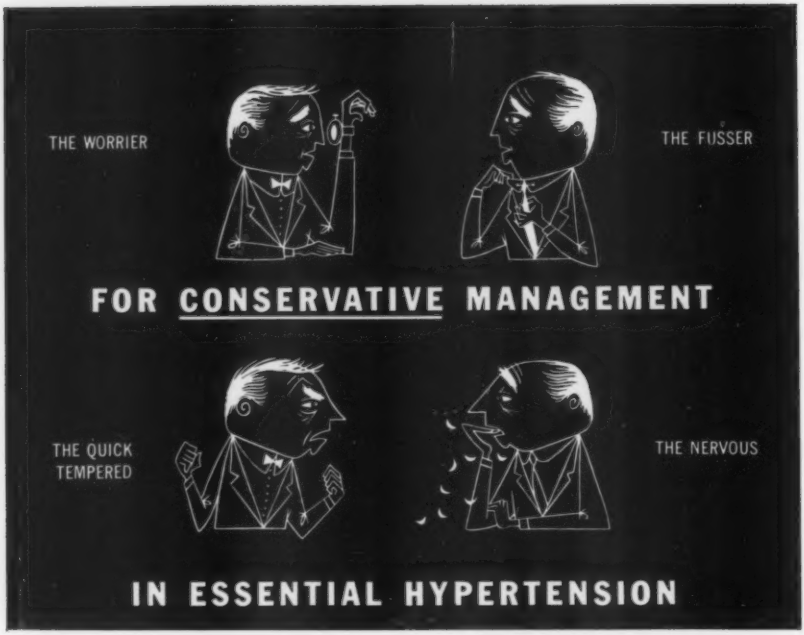

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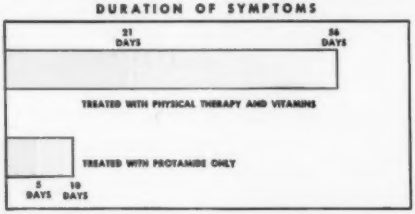

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Neurology

The Changing Front of Research on Poliomyelitis

Henry W. Kumm, M.D.

DURING THE 15 YEARS since the National Foundation for Infantile Paralysis was founded, its research program, originally directed toward the epidemiology and treatment of this disease, has gradually expanded to include intensive studies of etiology, pathogenesis, epidemiology, better methods of diagnosis and treatment, and finally prevention. In the present paper brief comment will be made on some of the significant advances achieved in each of those fields.

ETIOLOGY

Since 1948 marked progress has been made in obtaining a clearer understanding of the etiology or cause of poliomyelitis. An approach which has proved to be unusually helpful has been the typing program. This was begun in 1948 and completed five years later. It indicated that the poliomyelitis viruses, which incidentally are world-wide in distribution, can be separated into three broad antigenic groups or types.[1,2] Among 196 strains which were so classified, 161 or 82 per cent were found to belong to Type 1; 20 or 10 per cent to Type 2; and 15 or 8 per cent to Type 3.

Each type is capable of causing paralytic poliomyelitis in the human being and of inducing a type-specific immunity. A patient who has recovered from

From the National Foundation for Infantile Paralysis, New York City.

Read at the sixth annual meeting of the American Academy of Neurology, Washington, D. C., April 30, 1954.

an attack with one type of poliomyelitis virus remains susceptible to infection with the other two types. Fortunately, however, only very few individuals actually develop paralysis as a result of successive attacks with more than one type of virus.

The discovery that there are three different types of poliomyelitis virus is of fundamental importance, because a vaccine to be effective will have to bring about immunity against all three types of the virus.

In November 1953 it was reported by Stanley, Bachrach, and Schwerdt[3,4] that they had successfully purified and concentrated strains of Type 2 poliomyelitis virus by treatment with butanol and enzymes. The strains of virus investigated by them were derived from the central nervous system of cotton rats and from infected cultures of monkey kidney tissue. The specific infectivity of their concentrated material was increased by some 20,000 times above that of the original infected tissues. Electron microscope studies of these poliomyelitis virus preparations revealed numerous spherical particles 28 millimicrons in diameter.

Sabin, Hennessen, and Warren[5] have also obtained electron photographs of poliomyelitis virus of Types 1 and 3, the latter being somewhat larger. It would appear, therefore, that at long last satisfactory photomicrographs of all three types of this virus have been achieved.

PATHOGENESIS

Considerable progress is also being made in clarifying the pathogenesis of poliomyelitis, that is to say, the sequence of events following infection in a human being or an experimental animal.

At one time it was thought that this virus entered the human body through the nose and reached the brain via the olfactory lobes. While this concept appears to be essentially correct for rhesus monkeys infected by intranasal instillation of virus, recent findings suggest that the mechanism in man may be quite different. It now seems likely that poliomyelitis virus gains entrance to the human body through the mouth or nose, and after a limited alimentary phase it may reach the central nervous tissues either by way of the blood stream or by migration along nerve fibers.

The possible existence of a vascular phase had long been disregarded because of almost uniformly negative findings when blood samples were tested for viremia at the onset of paralysis in man. By the time paralysis had supervened, antibodies were already present in abundance in the peripheral circulation. Prior to 1952 medical literature contained only two records of viremia in human poliomyelitis infections, one of them a girl nine years of age and the other a 29 year old man.

New evidence has been presented recently concerning the occurrence of a vascular phase in the experimental disease in cynomolgus monkeys and chimpanzees. Investigators working independently at two universities[6,7] reported the finding of poliomyelitis virus in the blood stream of such animals from four to six days after being fed the virus.

During the brief stage of viremia antibodies are rapidly formed so that they are present in abundance at the onset of paralysis. While it is likely that virus penetrates the central nervous system during the stage of viremia, the mechanism governing such penetration is unknown at present. In monkeys the interval between the appearance of virus in the blood stream and the subsequent development of paralysis varies between three and seven days.

Additional data concerning viremia in man were secured from field studies carried out in the summer of 1952.[8,9] Ten children suffering from minor illnesses later diagnosed as abortive cases of poliomyelitis and one infant with no symptoms whatsoever were found to have virus of Type 1 circulating in their blood streams. If a brief stage of viremia were a constant finding in human beings, it would be easier to understand why antibody in the form of gamma globulin, when administered at a critical time just prior to viremia, might facilitate the process of natural immunization without permitting the development of paralytic symptoms.

EPIDEMIOLOGY

Many careful studies of the epidemiology of poliomyelitis have been carried out in the past and as a result satisfactory explanations have been obtained for some of the characteristic features of this disease. Other aspects, however, are still obscure. One of these is the typical seasonal distribution. We still do not know why approximately 80 to 90 per cent of the cases in temperate zones occur during a period of four or five months which includes the summer and early autumn.

One of the more striking facts in the epidemiology of this disease is the regularity with which most members of a family become infected within a few days of one another and are found to be simultaneous carriers of the virus. There are a number of possible explanations for this interesting phenomenon and which of them is correct is at present unknown.

In poliomyelitis we have the paradox of more paralytic disease in those parts of the world where there is less virus and a lower incidence where the virus is most freely distributed. Adults living in regions of primitive sanitation where paralysis is rarely reported almost invariably have poliomyelitis antibodies in their blood, and they have generally acquired such immunity at a relatively early age with no recognizable symptoms.

It appears that immunity in most adults is gained at the price of about one paralytic illness per hundred nonparalytic or abortive infections. Meticulous examinations of sera collected at Winston-Salem, North Carolina, during the epidemic of 1948 have shown that, among children up to 14 years of age, the number of subclinical infections per case varied between 62 and 175 in the different age groups.[10] During that outbreak children developed antibodies against virus of both Types 1 and 2.

Recently an attempt was made to calculate the risk of contracting poliomyelitis.[11] In four representative states from which statistical information was available, it appeared that among the children born in 1930, 1931, or 1932

one out of every 156 acquired this disease during the first 20 years of life. In those same groups of children, one out of every 1,945 died from infantile paralysis before reaching the age of 20.

DIAGNOSIS

Typical cases of infantile paralysis are readily diagnosed on clinical grounds alone, but in atypical or abortive cases it may be necessary to resort to laboratory procedures such as isolation of the virus or studies of serum antibodies. For many years, monkeys inoculated intracerebrally were used almost exclusively for such investigations. Since these animals are all imported from the orient, isolations of virus or titrations of antibodies in them are expensive procedures.

In 1949 and 1950, however, an epoch making advance, which may in time prove to be the keystone of modern research on poliomyelitis, was made when Enders, Weller, and Robbins[12,13] discovered that all three types of this virus could be cultivated on small pieces of certain human or animal tissues growing in test tubes. In a suitable nutrient medium, poliomyelitis virus will multiply on cells growing out from small fragments of human embryonic skin-muscle, adrenal, heart, intestine, kidney, prepuce, spleen, testis, thyroid, tonsil, and uterus, and also on monkey intestine, kidney, lung, muscle, and testis.

One of the useful tissue culture systems is a roller tube culture. This is nothing more than a test tube, on the inside of which little pieces of certain monkey or human tissues have been distributed in a sticky film of plasma. Afterwards salt solution, horse serum, beef extract, chick embryo extract, or a synthetic medium such as mixture No. 199 of Morgan, Morton, and Parker[14] is added. These tubes are then placed in a drum inside an incubator. As the drum revolves slowly, it causes the nutrient medium to wash over the little pieces of living tissue. Soon cells begin to bud out and grow over the entire inner surface of the test tube. It has also been found that for certain types of work, stationary tubes are just as satisfactory as roller tubes. The rolling mechanism, therefore, does not appear to be essential. After the new cells are growing well, the addition of a small amount of poliomyelitis virus will cause them to die. This phenomenon can be seen easily in a microscope.

If type-specific antibody derived from a patient who has recovered from an attack of poliomyelitis is added, those living cells will not die. It is now possible to isolate a strain of virus or to carry out a neutralization test in a test tube culture costing less than 50 cents instead of using a live monkey valued at more than 35 dollars. A recent report by Youngner[15] indicates that the use of a standardized suspension of trypsinized monkey kidney cells is an excellent method for preparing large numbers of replicate tissue culture tubes suitable for such virus isolations.

For some time it has been realized that if a pure genetic line of cells uniformly susceptible to the poliomyelitis viruses could be found, tissue culture technics would be further simplified. Variations in the relative susceptibility

of different types of tissues and of tissues originating from different animals or different human beings would thereby be avoided.

For that reason a recent discovery made at the University of Minnesota is of unusual interest.[16] A strain of epithelial cells derived from a carcinoma of the human cervix has been carried continuously in tissue culture since February 1951. The patient from whom this strain was obtained, a colored woman who lived in Baltimore, died six months later, but the HeLa strain of cells which bears her name lives on in poliomyelitis laboratories all over the world. Cells of this strain grow readily on glass surfaces, even in the absence of plasma, and they are easily maintained by serial cultivation in vitro. When inoculated with poliomyelitis virus, cytopathogenic alterations become evident in from 12 to 72 hours.

This strain is of particular value for isolating and typing new strains of virus derived from patients and for measuring levels of antibody in the circulating blood. During the past year and a half, 300 strains of virus from patients admitted to hospitals in Minnesota and Iowa have been isolated and typed by this new technic. Among them 74.5 per cent belonged to Type 1, 5 per cent to Type 2, and 20.5 per cent to Type 3.[17]

Strains of all three types of the virus, adapted to growth in tissue culture, have also been employed as antigens in complement fixation tests for the diagnosis of poliomyelitis.[18] This is a reaction similar to the well known Wassermann test for the diagnosis of syphilis. Complement-fixing antibodies were demonstrated in the serum of patients with infantile paralysis, as well as in hyperimmunized monkeys. Sera obtained from patients a year or more after termination of their respective illnesses, when tested at the same time as earlier specimens, have shown a marked drop in the concentration of complex-fixing antibodies.

The presence of a positive complement-fixation test as well as a positive neutralization test is therefore suggestive of a recent infection. Conversely, if the neutralization test is positive and the complement-fixation test negative, it is probable that the infection in that individual occurred in the more distant past. There are, of course, many situations in which it would be advantageous to be able to determine whether or not a recent illness actually was poliomyelitis. This work, while promising, has not yet been developed to the point where a practical complement-fixation test is available for widespread use.

TREATMENT OF PATIENTS

The problems of medical care and treatment have been multiplied many times by recent years of high epidemic incidence. In this situation, overhospitalization has constituted one of our perplexing problems. Some physicians who fear that they will be blamed if paralysis ensues have recommended hospitalization of all early cases. With little or no cost deterrent, numerous patients, therefore, entered hospitals even though they could have been treated equally well at home. Unnecessary hospitalization, however, results in over-

crowding, which handicaps the hospital's ability to provide good care for critical cases or for severe paralytics. It has been stated recently by Stimson[19] that most patients with suspected poliomyelitis and many others with the milder types of this disease can be better cared for at home. An additional advantage is that the family physician remains in touch with his own patient.

Somewhere between 15 and 20 per cent of diagnosed cases develop respiratory difficulties either from bulbar or from bulbospinal involvement. About half of them require the temporary use of a respirator. While milder cases usually recover after limited periods of special treatment, it is the chronic respirator patient who constitutes one of our most difficult problems. Since there are approximately 1,500 patients now living in iron lungs in this country, intensive study is underway aimed at developing improved methods of caring for these helpless patients. Group care in hospitals can be furnished to such patients at reduced cost, because essential nursing services can then be shared among all members of the group.

A number of regional respirator centers have been established in teaching hospitals in the States of California, Illinois, Massachusetts, Michigan, Nebraska, New York, Texas, and Washington. Those centers provide many services, including evaluation and treatment for groups of respirator patients, clinical investigation, teaching and training for physicians, nurses, and physical therapists, and finally consultation services to hospitals and physicians. Encouraging results are being obtained in the rehabilitation of many of the more seriously paralyzed cases.

At the present time there is no known drug which is effective either for the prevention or the treatment of poliomyelitis. More than 800 substances have been tested in the past and a continuous search for such an agent is still proceeding.

Before the discovery of methods for growing poliomyelitis virus in test tubes, we had no cheap or efficient laboratory procedure for selecting among the thousands of promising chemical compounds those particular substances which merited further critical trial in experimental animals. One of the grantees of the National Foundation for Infantile Paralysis is now carrying out an extensive screening program using tissue culture methods. Each substance is first tested for toxicity to tissue culture cells, and then its potentialities as an inhibitor of poliomyelitis virus growing in tissue culture are investigated. Substances showing positive effects are subsequently tested in cynomolgus monkeys infected orally.

PREVENTION

There are two immunologic mechanisms by which individuals can be protected against developing the paralytic form of this disease. These involve either passive or active immunity. In the case of the former, adequate levels of serum antibody may be attained temporarily by inoculation of materials containing antibodies in high titer, such as gamma globulin. Production of active immunity, on the other hand, requires the injection of virus either in

a modified or inactivated form, so that the host himself does not succumb, but instead produces specific neutralizing antibodies in abundance.

It has been shown experimentally that transient passive immunity will protect monkeys and chimpanzees from developing paralysis when challenged by peripheral administration of virus. Further studies were, therefore, planned to determine whether passive immunization of children would likewise prevent the development of paralysis in them. For that purpose, extensive field trials with a promising blood fraction were conducted in 1951 at Provo, Utah, and in 1952 at Houston, Texas, Sioux City, Iowa, and South Sioux City, Nebraska.[20 21]

In all a total of 54,772 children were inoculated, of whom half received gamma globulin and the other half were given gelatin. The clinical investigators were not aware which substance had been inoculated into each child until after the study had been completed. The dosage of gamma globulin used was 0.14 cc. per pound of body weight, given intramuscularly.

A total of 104 cases of paralytic poliomyelitis occurred during the follow-up period of 14 weeks. For the first week after injection, differences in incidence between the two groups were not striking, though there was some evidence that the severity of paralysis might have been modified in the group inoculated with gamma globulin. From the second through the fifth week on the other hand, a significant, though not complete, degree of protection was demonstrated. Paralysis appeared in seven children who had received gamma globulin as compared to 39 who had been inoculated with gelatin.

During the sixth, seventh, and eighth weeks after injections, the protection afforded by gamma globulin appeared to be waning and no protection was detectable after the eighth week. It was also found that administration of gamma globulin did not prevent injected children, who subsequently became infected, from excreting virus in their stools and developing an active immunity to that particular strain. Protection from paralysis appeared to have been achieved with levels of antibody which were barely detectable by present day methods.

Because stocks of gamma globulin were not adequate for the inoculation of all children who were exposed during the summer of 1953 to infection with the virus of poliomyelitis, considerable discussion took place as to the best methods of allocating the available supply. The Office of Defense Mobilization assumed this responsibility and recommended two principal methods of administration, namely, mass immunizations and the inoculation of household contacts. It was hoped that as a result of experience gained during the summer of 1953 it might be possible to arrive at some conclusions as to the relative merits of each of these two systems.

To that end, a national advisory committee for the evaluation of gamma globulin was formed and a summary report prepared by that group appeared recently.[22] The total number of children inoculated in programs of mass immunization in 1953 was close to 235,000. Projects of that type were carried

out in 22 counties and one city located in 13 states. Unfortunately from the standpoint of scientific study, in more than half of those outbreaks the size of the epidemic was too small or else inoculations were given too late to be effective. The committee members concluded from the results of their analyses that the data on mass prophylaxis collected in 1953 did not yield statistically measurable results. It is not felt, however, that this decision invalidates the findings from the original field trials conducted in 1951 and 1952.[20,21]

From their analysis of information assembled on the efficacy of gamma globulin when given to family contacts of patients, the committee decided that administration by this method with the preparations involved, and in the dosages used, had no apparent effect on the incidence or severity of paralysis developing in subsequent cases.

In this connection it may be of interest to recall certain statements made by Hammon[23] on the basis of his studies in Iowa, Texas, and Utah. He has indicated that a passive immunizing agent, such as gamma globulin, has only a limited field of practical usefulness. Because it is in short supply, and also because it appears to be necessary to inoculate very large numbers of children for each paralytic case prevented, an effective vaccine will provide a better solution to this problem in due course.

There are a number of different ways in which a satisfactory vaccine might be prepared. These include inactivation by chemicals or other agents, serial passage of the virus through some unnatural host, or administration of adequate amounts of immune serum followed by virus.

It seems appropriate to discuss inactivated vaccines first. Recent reports by Salk[24,25] indicate significant progress towards developing an inactivated poliomyelitis vaccine. Representative strains of each of the three immunogenic types of the virus are propagated in cultures of monkey kidney tissue, using as a nutrient medium synthetic mixture No. 199. The virus is inactivated with formaldehyde. Absence of infectivity is then verified by tissue culture technics, as well as by intrathalamic and by intramuscular inoculations of the vaccine into monkeys. It was found that the immunogenic potency of the vaccine could be increased by giving three successive inoculations of an aqueous preparation, the third after an interval of four weeks. Antibody levels induced by such vaccinations compare favorably with those which develop following natural infection with the virus.

To date a total of more than 5,000 children have been inoculated by Salk in Allegheny County, Pennsylvania, without any bad effects, using a vaccine prepared in his own laboratory. An additional 4,000 youngsters have received a similar vaccine prepared by a commercial company. Immunity produced appears to have lasted for at least seven months. The results of these studies provide justification for optimism, though we do not yet know whether Salk's inactivated poliomyelitis vaccine will protect against the disease occurring under natural conditions. A definite answer to that important question should be forthcoming from the extensive field trials now underway.

Encouraging progress has also been reported recently by Milzer and coworkers[26] in their attempts to immunize human beings with a trivalent vaccine inactivated by ultraviolet light. They have employed both adjuvant and aqueous vaccines. Only minimal reactions were encountered among 34 volunteers inoculated so far.

Serial passage of poliomyelitis virus through unnatural hosts is another promising approach to this problem. It will be recalled that a number of good vaccines against virus diseases of man and animals have been prepared from strains of live virus adapted to propagation in unnatural hosts. The vaccine for yellow fever comes to mind in this connection. Yellow fever virus, after hundreds of serial passages in monkeys, mice, tissue cultures, and finally chick embryos, became so modified that on peripheral inoculation lost its lethal attributes for man but continued to maintain its capacity to induce immunity.

It has been reported by Enders and associates[27] that the pathogenicity for mice of a strain of Type 2 poliomyelitis virus had become reduced by prolonged cultivation in cultures of human tissues. Likewise, a decrease in infectivity for monkeys was observed in a strain of Type 1 virus which had been treated similarly.

Sabin[28] has found that by rapid serial passage of large amounts of virus of Types 1 and 2 growing in cultures of kidney tissue, he has been able to produce variants with diminished virulence for the central nervous system of cynomolgus monkeys.

Finally, a group of workers at Lederle Laboratories[29] have reported that the MEF_1 strain of human poliomyelitis virus, a Type 2 strain, has become adapted to propagation in developing chick embryos following 119 serial passages in suckling hamsters. After from 38 to 40 consecutive passages in such embryos, the identity of this adapted strain with poliomyelitis virus was confirmed by cross neutralization tests. Monkeys and chimpanzees which received intramuscular or oral inoculations with this strain were reported to be immune to subsequent challenge with homologous virus.

It is important to remember in this connection that no strains of Type 1 or Type 3 have yet been adapted to passage in chick embryos. Furthermore, Types 1 and 3 appear to be responsible for most human cases of poliomyelitis. Therefore, to be really effective, such chick embryo adapted live virus vaccine would have to be polyvalent or, better still, trivalent.

SUMMARY

In summary we can say that considerable progress is being made in obtaining clearer concepts of the etiology, epidemiology, and pathogenesis of poliomyelitis, as well as in devising better methods of diagnosis, preventing paralysis, and improving medical care. The increased tempo of progress that has occurred in the last few years is largely due to the crucial discovery made by Enders and his colleagues that the poliomyelitis viruses can be grown in cultures of non-nervous tissues.

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Intolerance of the Primate Brainstem and Hypothalamus to Conventional and High Energy Radiations

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SHORTLY AFTER STUDIES of the effects of various radiations upon the central nervous system of monkey and man were begun in 1949, it was noted that the brainstem and hypothalamus were rather intolerant to large doses of x-rays from conventional x-ray equipment and to biologically equivalent doses of high energy x-rays from the betatron.[1–3] A similar intolerance of these areas to equivalent dosages of high energy electrons has also been observed in studies of 17 mev (million electron volt) electrons from the betatron on the brains of monkeys.[4] This intolerance of the brainstem and hypothalamus of monkey and man to a variety of radiations becomes an important consideration in the planning of radiation therapy for patients with neoplasms of the central nervous system, particularly for those patients with neoplasms within or about the central axis of the brain.

Both the brainstem and hypothalamus are quite radio-responsive. Radiation effects can be observed promptly after moderate dosages of irradiation and at prolonged intervals of time after irradiation, when delayed radiation damage may appear. Both the acute and delayed reactions may seriously alter the course of the patient's life.

The intolerance of the brainstem and hypothalamus to large doses of radiation appears to be due to two factors: 1) these areas subserve many functions essential for survival, and 2) these areas are much more radio-responsive than cortical areas. The much greater responsiveness of the brainstem and hypothalamus to irradiation will be demonstrated in this paper, and the clinical importance of these observations will be discussed.

LITERATURE

No systematic studies of the effects of radiation on the brainstem or hypothalamus of primates have been reported other than those of the authors.[1–3]

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A very interesting observation was made by Ellinger[5] and by Davison and Ellinger,[6] who observed in total-body irradiated goldfish that pronounced radiation changes occurred in the medulla oblongata. They postulated that x-rays caused damage to a chromatomotoric nerve center located in the medulla oblongata, which in turn was the cause of roentgen pigmentation in the goldfish.

METHOD OF STUDY

In all animal studies, as well as in irradiation studies of patients with central nervous system neoplasms, precision localization of the radiation was carried out and the tissue and tumor dosages were carefully computed. Irradiated tissues for study were obtained at autopsy in experimental animals and at surgery or at autopsy in our patients. All tissues were sectioned serially and prepared for study by a variety of neurohistologic methods.[1–4] The primate brainstem and hypothalamus have now been observed to be responsive to moderate doses of conventional x-rays, high energy x-rays, and high energy electrons. Since the best data have been obtained with the well defined, homogeneous, and penetrating beams of high energy x-rays (23 mev) produced by the betatron, a few comments on the experimental methods of irradiation with high energy x-rays will be given, which will obviate to a certain degree the necessity of referring to previous publications.

In general, small (1.0 cm. or 2.5 cm.) circular beams of high energy x-rays were fired transfrontally or transtemporally across the head of the monkey. A wide range of single doses from 375 r to 14,000 r of 23 mev x-rays have been studied in a large series of monkeys. This dose-range of 375 r to 14,000 r of 23 mev x-rays is equivalent in biologic effectiveness to from 225 r to 8,400 r of 400 kv x-rays.* It is possible with the betatron to place a nearly uniform dose of x-rays across the monkey's brain by the technics employed in these studies. The reader is referred to reference 2, which gives the full details of how the normal dose-distribution of the high energy x-rays was altered to obtain the uniformity of dose throughout the irradiated brain of each monkey. By actual determination the skin dose on the entry side of the beam was 100 per cent of the total dose and the skin dose on the exit side was approximately 90 per cent of the total dose administered. With such uniformity of dose-distribution obtainable with high energy x-ray beams from the betatron, one can readily compare the degree of responsiveness of the various cerebral areas in the field of irradiation and clearly demonstrate that certain regions of the brain, such as the brainstem and hypothalamus, are more responsive than cortical areas. Small beams of x-rays were employed rather than total-head irradiation so that there would be considerable non-irradiated tissues in the same or adjacent sections to serve as a control for the irradiated areas. The monkeys were then sacrificed at selected intervals over a period of three

*High energy x-rays have been demonstrated to be less effective quantitatively than low energy x-rays from a biologic standpoint, but the exact coefficient of biologic effectiveness is still a matter of dispute. In our studies a factor of 0.60 has been used.

years. The single doses of irradiation (as related to time) which would cause delayed radionecrosis of the brainstem were determined. The acute lethal dose for the brainstem was also determined.

More recent studies have been undertaken to determine the effect of fractionated courses of high energy x-rays on the central nervous system of the monkey. These courses will simulate the degree of fractionation and the total tumor doses employed in clinical radiation therapy of neoplasms of the central nervous system.

OBSERVATIONS

Observations on the effects of radiation on the brainstem of the monkey

When a single dose of 3,000 r of 23 mev x-rays (equivalent to 1,800 r of 400 kv x-rays) is fired across both temporal lobes and brainstem a very striking delayed radionecrosis of the brainstem develops at approximately six to eight months after irradiation. The appearance of this delayed radiation damage to the brainstem can be seen in figure 1. It is to be noted that no gross damage is present in either temporal lobe, although microscopic changes can be detected. As indicated under experimental methods, it is technically possible with the betatron to deliver a uniform dose of x-rays throughout the desired areas. Therefore, since both temporal lobes and the brainstem received almost equally 100 per cent of the 3,000 r of 23 mev x-rays (equivalent to 1,800 r of 400 kv x-rays) it is obvious from this photograph that the brainstem is much more radio-responsive than the temporal lobes. Under higher magnification (figure 2) the intense degree of radiation damage to the brainstem can be more readily observed. (In this section of the brainstem, the corticopontine and corticospinal bundles and the decussation of the brachium conjunctivum are most seriously injured. Compare with a normal brainstem, figure 3). Microscopically, radiation effects are present in the neuronal and glial elements as well, but the damage to the fiber tracts (that is, myelin and

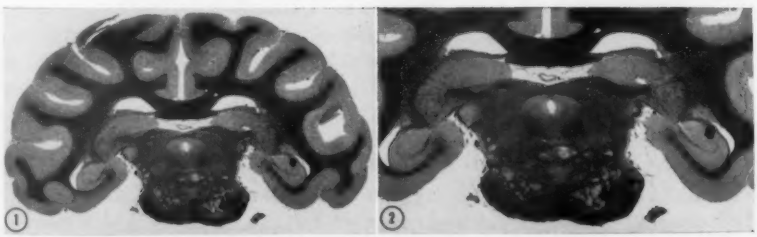

FIG. 1. Appearance of delayed radionecrosis in brainstem of a monkey at six months after irradiation with 3,000 r of 23 mev x-rays. Both the temporal lobes and the brainstem received the same dose of x-rays. Note, therefore, that the brainstem is more radio-responsive than the temporal lobes. Weil preparation.

FIG. 2. Same section as figure 1 under higher magnification to show extensive damage to the decussation of the brachium conjunctivum and the corticopontine and corticospinal bundles of the brainstem. Weil preparation.

axons) is by far the most outstanding pathologic finding. The insignificant vascular changes cannot conceivably account for the damage to the neural elements. Monkeys irradiated with this dose develop a quadriparesis at approximately five months postradiation. Abnormal electrical activity in the form of discrete spikes or spike-and-wave formations have been observed in both temporal lobes by electroencephalographic studies prior to the appearance of neurologic signs. Overt clinical seizures may be present for a few weeks prior to the death of the monkey. Death occurs at six to eight months after radiation in all monkeys when irradiated through the brainstem with 3,000 r of 23 mev x-rays (equivalent to 1,800 r of 400 kv x-rays).

When a single dose of 1,500 r of 23 mev x-rays (equivalent to 900 r of 400 kv x-rays) is fired across the temporal lobes and brainstem the monkey continues to survive beyond six or eight months but eventually develops a moderate hyperreflexia of all extremities at a year or more postradiation. Electrical abnormalities can be detected quite early after radiation even with this relatively low dose of high energy x-rays. Histologic examinations of these monkeys sacrificed at 12 months or 18 months after radiation have shown maximum radiation effects in the brainstem, but the pathologic alterations were much less in degree than observed with the larger doses of high energy x-rays (figure 4). (Compare with a normal brainstem, figure 3). Whether these monkeys which have been irradiated through the brainstem with 1,500 r of 23 mev x-rays will eventually succumb with the further passage of time remains to be seen.

When single doses of 5,000 r of high energy x-rays (equivalent to 3,000 r of 400 kv x-rays) are fired across the brainstem death usually occurs in one to three days as a result of the acute radiation damage. With such large single doses of radiation there is no evidence of radioselectivity for any areas of the central nervous system, since all areas are seriously affected.

Observations on the effects of radiation on patients with neoplasms in or about the brainstem

Three patients have been observed in whom delayed radionecrosis appeared in the brainstem at intervals of one year or more following therapy. Two of these patients had been treated with 400 kv x-rays and each had received a tumor dose of 4,500 r in 30 days for a brainstem glioma. The third patient had been given therapy with 23 mev x-rays from the betatron for an ependymoma of the fourth ventricle which could not be adequately excised. The patient received a tumor dose of 7,500 r of 23 mev x-rays (equivalent to 4,500 r of 400 kv x-rays) in 18 days which completely relieved his neurologic difficulties, and he remained asymptomatic for 13 months, at which time extensive signs of brainstem disorder appeared. The patient then succumbed in a few weeks. In all three cases the duration of survival was lengthened by the radiation, and histologic examination at autopsy showed that the tumors of all three patients had been extensively affected by the radiation. Only very small foci of recurrent tumor or residual tumor were evident in

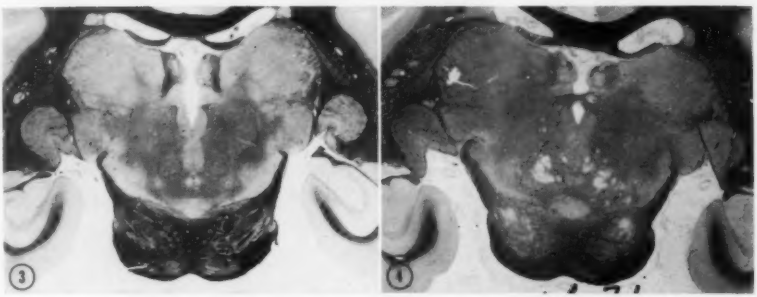

FIG. 3. Normal brainstem of nonirradiated monkey for comparison with figures 1, 2, and 4.

FIG. 4. Response of the brainstem at six months after subjection to 1,500 r of 23 mev x-rays. The degree of radiation damage is much less than that obtained with 300 r. Note the symmetry of response. Weil preparation.

each case. However, very marked degenerative changes of the fiber tracts and cellular constituents of the brainstem occurred also which were the result of the radiations.

Observation on the effects of radiation of the hypothalamus of the monkey

The hypothalamus of both monkey and man proves to be radio-responsive. It responds in a very unusual fashion in that the cells of the paraventricular and supraoptic nuclei are selectively affected by small doses of radiation, whereas the other cellular components of the hypothalamus show only mild changes. These irradiation effects can be detected promptly after radiation, but are most striking at prolonged intervals of time after radiation.

The paraventricular and supraoptic nuclei are readily identifiable cellular structures within the hypothalamus and their cells have been known for some time to be concerned with the conservation and distribution of body water,[7] and more recently perhaps with the partial control of the thyrotropic[8] as well as the adrenotropic hormones.[9] Figure 5 shows the normal appearance of the paraventricular nuclei of the nonirradiated hypothalamus of an adult monkey. By contrast, figure 6 reveals the effects of x-irradiation on the paraventricular nuclei of a monkey which had been sacrificed at six months after the administration of 3,000 r of 23 mev x-rays (equivalent to 1,800 r of 400 kv x-rays). It is to be noted that the paraventricular nuclei are selectively affected by radiations, whereas only very mild histologic changes were noted in the other cells of the hypothalamus. The supraoptic nuclei were altered just as severely by the radiations but these nuclei are not shown in this photograph.

This selective effect of x-irradiation on the paraventricular and supraoptic nuclei of the hypothalamus has been noted to a lesser degree in monkeys receiving 1,500 r of 23 mev x-rays (equivalent to 900 r of 400 kv x-rays).

When single doses of 23 mev x-rays above 3,000 r are given the entire hypothalamus is diffusely damaged and the cortical areas traversed by the

radiations are affected as well. Hence, there is no evidence of radioselectivity in the hypothalamus with dosages above 3,000 r of 23 mev x-rays. With single doses of 3,000 r or less it can be readily shown that the nuclear masses of the hypothalamus are much more responsive than the cortical areas which received the same dose of x-rays. The significance of this observation will be brought out under the discussion of this report.

The mechanism for this selective effect of x-rays upon the paraventricular and supraoptic nuclei would appear to be a degenerative effect resulting from the radiation itself. In figure 7 the microscopic appearance of the normal cells of the nonirradiated paraventricular nucleus can be seen. The normal adult cells of the paraventricular and supraoptic nuclei have a rather clear, oval to rounded nucleus, with a heavily staining nucleolus. These cells possess very prominent Nissl bodies within their cytoplasm which are distributed rather unusually when compared with the neurons of the cerebral cortex, in that their Nissl bodies are distributed peripherally against the cell wall and give the cell the appearance of a neuron undergoing early chromatolysis. This peripheral distribution of the Nissl material is, however, a normal condition for these cells. By contrast the irradiated hypothalamic nuclei, when examined at five to six months after radiation, show a considerable deficit in number of cells and all the surviving cells present marked degenerative changes (figure 8). Some of the residual cells appear as bare nuclei devoid of any cytoplasmic envelope. Other cells are abnormally large or deformed. A considerable degree of nuclear and cytoplasmic vacuolation occurs. Very little reactive gliosis appears about the affected areas.

Observation on the effects of radiation on the hypothalamus of man

Observations on the effects of radiation on the nuclear masses of the hypothalamus of man are inadequate as yet. Too often the irradiated lesion in the region of the sella or hypothalamus creates compressive changes or retro-

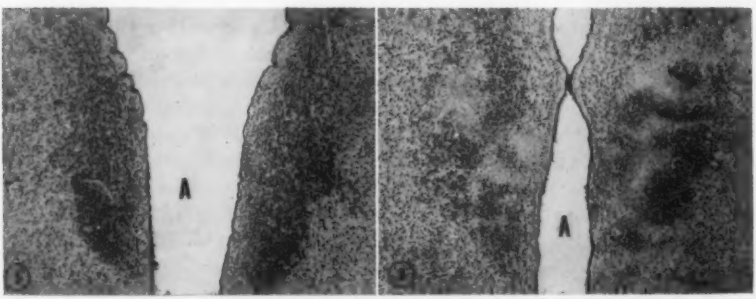

FIG. 5. Appearance of the paraventricular nuclei of the hypothalamus in a normal nonirradiated monkey. *A*—third ventricle. Thionin preparation.

FIG. 6. Demonstration of the *selective* and extensive damage to both paraventricular nuclei in a monkey sacrificed six months after 3,000 r of 23 mev x-rays. The supraoptic nuclei were just as severely affected but are not shown in this figure. *A*—third ventricle. Thionin preparation.

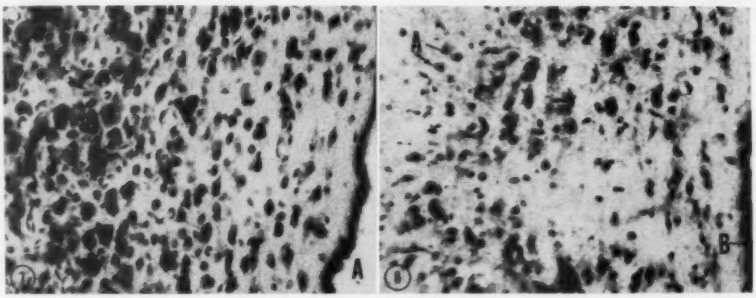

FIG. 7. The appearance under high magnification of the normal cells of the paraventricular nucleus from a nonirradiated monkey. Note the peripheral distribution of the Nissl granules which is a normal condition for these cells. *A*—third ventricle. Thionin preparation.

FIG. 8. Demonstration of the severe degenerative changes following x-irradiation observed in a monkey sacrificed six months after receiving 3,000 r of 23 mev x-rays. Note the severe cellular changes. *A*—degenerate cells which have lost their cytoplasm and appear as bare nuclei. *B*—ependymal surface of third ventricle. Thionin preparation.

grade cell reactions in the hypothalamic cell masses under study which interfere somewhat with the interpretation of the radiation effects. However, by careful examination of serial sections of blocks of the entire tumor and hypothalamus it has been possible to dissociate some of the cell changes due to radiation from the cellular changes due to compression. In the future, hypothalamic tissues will be obtained from patients who are receiving experimental x-ray therapy directed to the pituitary-hypothalamic region in an effort to obtain some palliation for widely disseminated cancers, such as carcinoma of the breast and melanoma, which are under hormonal control. The examination of tissues from such cases will be subject to less criticism and will yield more accurate information, since there will be no local lesion present to distort the pathologic picture created by the radiation.

DISCUSSION

From experimental studies and observations on patients undergoing radiation therapy, it would appear that the brainstem and hypothalamus are radioresponsive. These observations are in contradiction to the commonly accepted concept that the central nervous system is generally radio-resistant. In addition, it has been demonstrated that the brainstem and hypothalamus are more radio-responsive than the cerebral cortical tissues.

The observation that the brainstem responds to moderate doses of radiation and is therefore intolerant of large doses of radiation predicates certain considerations of practical importance in tumor therapy and some theoretical potentialities in atomic radiations.

The brainstem in brain tumor therapy

Tumors originating within the brainstem cannot be extirpated for obvious reasons, and frequently tumors arising within or about the fourth ventricle,

the thalamus, and the deep cortical areas cannot be adequately or completely excised. Consequently patients with such lesions are subjected to deep x-ray therapy, and rightly so since considerable palliation may be obtained with x-ray therapy in many cases. Patients with highly malignant lesions of these areas seldom survive more than a few weeks without therapy. With tumor dosages of 4,000 r to 5,000 r given in four to six weeks, useful palliation for an additional few months may be obtained in some cases. In such cases the potential appearance of a delayed radionecrosis of the brainstem at intervals of a year or more after radiation need not be feared since these patients with malignant lesions seldom survive over a year, even with radiation therapy. An exception to this last statement is the possibility of obtaining survivals much over a year in patients with medulloblastomas.

On the other hand, it would appear to be inadvisable to give large doses of radiation as are often given to patients with slowly growing neoplasms located within or about the vicinity of the brainstem. Such lesions frequently possess long innate survival times beyond a year. Excessive radiation therapy may, therefore, hasten the demise of these patients in view of the intolerance of the brainstem to large doses of radiation. In cases of benign lesions, such as ependymomas or astrocytomas, a surgical decompression and surgical relief of obstruction, if present, should be carried out. Ample biopsy tissue should be obtained if possible for histologic study and, if radiation therapy is to be given, a tumor dose of less than 4,500 r in four to six weeks should be given. In these cases 3,000 r delivered to the tumor in four weeks we believe would be a dose which may afford some inhibition of tumor growth and yet will not give rise to a delayed radionecrosis of the brainstem. Some brainstem and thalamic gliomas, as well as cerebellar astrocytomas, progress so slowly that it would appear unnecessary to administer any radiation therapy at all immediately postoperative. Radiation therapy would be reserved for such lesions whenever symptoms recurred and the lesion was beyond surgical control.

It would, therefore, appear that most lesions in and about the brainstem are not radiocurable, since the optimal tumor dose required for the effective destruction of lesions in this region may be equal to or greater than tolerance of the brainstem. However, it would be therapeutically unwise to deny x-ray therapy to patients with such lesions after the surgical gains have been reaped since considerable palliation may be obtained in a few cases. At times the degree of useful palliation may be far in excess of that predicted for the activity of the lesion based on histologic examination.

We hope that in future reports we will be able to give more specific data on optimal tumor dosages for lesions within and about the brainstem after the lesions of larger numbers of patients have been studied before and after radiation therapy.

Significance of the brainstem in atomic radiations

When the total body of man or animal is exposed to a single dose of 200 kv x-rays, relatively small single doses of radiation are required to kill.

The approximate LD/50 dose for a variety of laboratory animals, including the monkey, ranges from 200 r to 800 r of 200 kv x-rays. In man the LD/50 dose of total body irradiation has been approximated at 400 to 800 r, which is comparable to the LD/50 dose for the monkey.

When the radiations, however, are restricted to a portion of the total body then the single dose required to kill increases many fold. From our experimental studies in the monkey it would appear that a single dose of 5,000 r of high energy x-rays (23 mev) or 3,000 to 4,000 r of low energies (400 kv) directed to the brainstem alone or to the entire brain will kill in one to four days. On the other hand much smaller single dosages of radiation will create serious degenerative changes in the central nervous system after the passage of many months and years. In the monkey, 1,500 r of high energy x-rays (23 mev) have been observed to produce changes in the brainstem at a year or more after radiation. Whether this single dose will eventually cause death of the animal has not been determined in view of the short period of observation, but it will definitely produce neurologic disturbances which can be detected by clinical examination and by electroencephalographic study. This dose of 1,500 r of 23 mev x-rays is biologically equivalent to approximately 1,000 r of 200 kv x-rays. Thus it would appear possible, principally on theoretical grounds, that a biologically equivalent tissue dose of gamma and neutron irradiation from an atomic blast could conceivably affect the brainstem of man seriously, provided the brunt of the exposure was to the head and the body was partially shielded. Obviously these are highly theoretical considerations inferred from our studies in the monkey and will, of course, have to be substantiated in man.

The hypothalamus and radiation

Our observation that the supraoptic and paraventricular nuclei of the hypothalamus can show degenerative changes following irradiation with moderate doses of x-rays may explain some of the clinical benefits obtained when radiation therapy is administered to the region of the hypophysis for the treatment of disorders related to pituitary dysfunction, such as malignant exophthalmos,[10] selected cases of hypertension,[11] and various gynecologic conditions when functional in origin, as in some cases of amenorrhea, oligomenorrhea, and sterility.[12–14] Whenever the therapist irradiates the pituitary region through the usual 5 cm. or 6 x 8 cm. cone, he unavoidably irradiates the hypothalamus since the close proximity of the two structures would allow them to fall into the field of irradiation of a 5 cm. or larger cone. Therefore, since the pituitary gland has been reported to be relatively resistant to radiation,* perhaps some of the benefits obtained by irradiating the pituitary-hypothalamic region result from the effects of the irradiations on the hypothalamic nuclei, which in turn exert a considerable control over the pituitary gland and its many functions.

*More careful studies, particularly long term studies, are necessary to be certain that the pituitary gland is radio-resistant since degenerative changes may possibly appear in the gland at long intervals after radiation.

Large doses of x-rays are being given in the pituitary-hypothalamic region to patients with diffuse malignancies which are under hormonal control, in an effort to determine whether any useful palliation can be obtained comparable to the palliation obtained in similar cases of diffuse cancers by surgical hypophysectomy. The dose required for such an effect remains to be determined. If the dose is relatively large, it may be excessive for the optimal tolerance of the hypothalamus for any long survival of the individual. But, even if one only obtained useful palliation for months or a year in hopeless cases of widespread malignancies, the investigation could be considered successful.

In general, we hope that carefully controlled studies in animals and patients such as we have undertaken will give us some basic knowledge which will enable us to treat less empirically and perhaps more successfully the many neoplastic disorders of the human brain.

SUMMARY

1. From experimental and clinical studies, the brainstem and hypothalamus of man and monkey appear to be intolerant to large doses of x-rays from conventional x-ray equipment and to biologically equivalent doses of radiations (x-rays and electrons) from the betatron.

2. The intolerance of the primate brainstem and hypothalamus to large doses of radiation is due to two factors: 1) these areas subserve many functions essential for survival, and 2) these areas are much more radio-responsive than cortical areas.

3. The primate brainstem and hypothalamus will also respond to moderate dosages of radiations.

4. The significance of these observations was then considered with respect to: 1) the brainstem in brain tumor therapy, 2) the possible potential damage to the brainstem in atomic radiations, when restricted to the head, and 3) the effects of x-irradiation of the pituitary-hypothalamic region on clinical disorders related to pituitary dysfunction.

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So far as pathology and experiment go, these deeper structures, at the level of the corpus striatum, or perhaps lower still, may be the parts which discharge in epilepsy. The fact that lesions in certain regions of the cortex cause convulsions beginning in certain parts, as the arm or the leg, is not incompatible with this view, since discharges beginning in the lower centres may have quite the same definite forms as when they are excited from the surface. Physiological considerations make it probable that the arrangement of represented movements in the lower centres is on the same plan as in the higher. Nor does the affection of consciousness afford valid ground for the assumption that epilepsy is a disease of the cortex, since those who believe that the discharge originates in the medulla find an explanation of the loss of consciousness by assuming an extension of the discharge to the vasomotor centre, causing arterial spasm throughout the brain. Even if we admit, for a moment, that there is no proof of arterial spasm, and that the overaction of motor gray matter is the only certain element in the convulsions, such overaction may disturb the centres above as well as the centres below, and, as Robertson of Glasgow has suggested, the loss of consciousness may be the effect of an upward discharge, just as the muscular spasm is the effect of the downward discharge. Thus, neither pathology nor experiment enables us to exclude the lower encephalic centres as the seat of the primary discharge in epilepsy; and, in the light of all known pathological and experimental facts, the latest writer of a systematic account of the disease, Nothnagel, can see no reason to modify the conclusion that the primary seat of the discharge – the seat of the disease –– is the convulsive centre in the medulla oblongata.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases,* published in 1885.

Investigation of the Primate Amygdala

Movements of the Face and Jaws

Maitland Baldwin, M.D., Laurence L. Frost, Ph.D. and Charles D. Wood, M.S.

IN MOST CASES of temporal lobe seizures which come to surgical treatment the significant pathologic lesion is inferior and mesial within the affected lobe. It usually involves uncus, hippocampus, amygdaloid nucleus, and the adjacent white matter, as well as the anterior portion of the first temporal convolution. This abnormality is a non-neoplastic gliosis which has been called "incisural sclerosis" in a previous report.[1]

The relationship of this abnormal sclerotic tissue to the epileptogenic processes may be established at operation by electrical stimulation and electrographic recordings. After it has been excised (and this excision is essential in most cases) chemical studies often confirm its epileptogenic characteristics.[2]

During surgical treatment of temporal lobe seizures we have explored this area with the stimulating electrode. This has been done in order to reproduce the auras and initial phenomena of the seizure pattern as well as the related electrographic abnormalities. The manner and the methods of this operative procedure have been described elsewhere.[3]

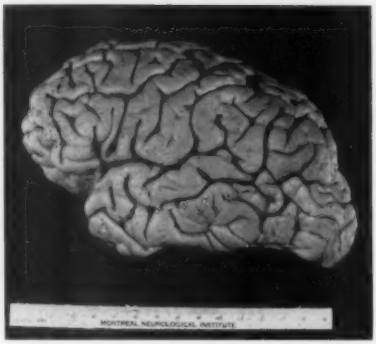
The operative anatomy and the means by which deeper structures may be reached with the stimulating electrode have also been described. However, this anatomy and that method are essential in the present discussion, since some of the details will be repeated.

Obviously the surgeon must orient himself to deeper structures by the use of surface landmarks, since both the most mesial aspect of the lobe and its deeper structures are hidden from view. He can do this by measuring backward along the midaxis of the lobe from its tip. This distance, from the tip posteriorly, is then divided at centimeter intervals. Each interval may be considered as a transection 1 cm. in thickness, which has been cut in a plane perpendicular to the midaxis (figure 1).

This cross-sectional anatomy is illustrated at the 4, 5, 6 and 7 cm. intervals in figure 2.

From the branch of surgical neurology, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda.

Read at the sixth annual meeting of the American Academy of Neurology, Washington, D.C., April 29, 1954.



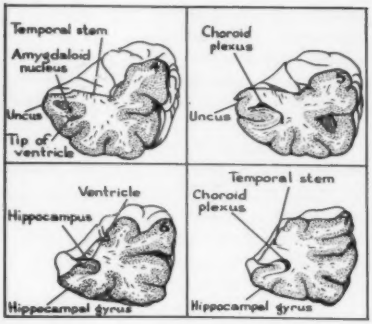


FIG. 1. (*left*) A brain with the pia removed demonstrates the position of the midaxis of the temporal lobe which has been divided into centimeter intervals as shown.

FIG. 2. (*right*) Transections of the human temporal lobe at 4, 5, 6, and 7 cm. intervals.

With this orientation the surgeon can introduce an electrode (insulated except at the tip) into uncus, hippocampus, or amygdaloid nucleus. The electrode is introduced through a small pial incision with the current off. At the desired depth the current is turned on. For example, the amygdaloid nucleus may be reached from a point close to the 4 cm. interval at a depth which varies from 3 to 4 cm. in a direction parallel to the superior surface of the temporal lobe.

In this manner we have stimulated the inferior and mesial regions of the temporal lobe in conscious, alert patients under local anesthesia. The following cases are examples.

Case 1.—A 25 year old housewife has had cerebral seizures for 16 years despite intensive medication. These attacks had a focal origin in the right temporal lobe. This was demonstrated by clinical and electrographic evidence. The initial phenomenon was alteration of consciousness in most attacks, but occasionally she noticed a palpitation in the epigastrium or "a peculiar thought like I was out of my mind." Either of the latter experiences might serve as a warning of the attack. During the seizure she became pale, smacked her lips, and salivated. There were movements of the left arm and occasionally she plucked at her clothing with both hands.

After an osteoplastic craniotomy the right temporal lobe was exposed. With stimulation at point 5 (6 volts, 60 cycles per second, 2.5 msec. duration) the patient said, "A drawing of the left side of my mouth."

The stimulating electrode was introduced through a pial incision at point 11 in a plane parallel to the superior surface of the temporal lobe. At a depth of 3 cm. a current of 6 volts, 60 cycles per second, 2.5 msec. duration, was turned on. A forward motion of the lower jaw was observed. This began promptly with stimulation and ended as the current was turned off. The patient tried to talk during this first deep stimulation. The word "jaw" was intelligible. Afterwards she said she felt movement in the right side of her face before it had been observed. The stimulation was repeated seven times with the same result.

Recording electrodes on the lateral and inferior temporal surface did not show any evidence of seizure discharge during or after stimulation. Likewise, scalp electrodes in

standard positions outside the surgical field did not reveal any electrographic abnormality during this deep stimulation.

Subsequently, during the excision of the anterior 5 cm. of this temporal lobe, the electrode tip was identified as it lay along the superior surface of the anterior end of the temporal horn. (We had severed the electrode rod from its glass holder and left it in place until excision.)

The location of the stimulation points and the approximate location of the electrode is illustrated in figure 3. This also illustrates the observer's description of the movements.

Case 2.—A 47 year old draftsman has had cerebral seizures several times each week during the past nine years. Clinical, x-ray, and electrographic evidence localized the origin of these attacks in the left temporal lobe. These seizures began with alteration of consciousness, followed by a stare and salivation. He has wandered aimlessly during some of them and is amnesic for these episodes.

During left osteoplastic craniotomy, stimulation at point 1 with 6 volts, 60 cycles per second, 2.5 msec. duration, was followed by a downward movement of the right lips. After the stimulation ceased the patient puckered his lips and licked them. He said he did this because "they felt funny."

The electrode was inserted at point 4 to a depth of 3 cm. in a direction parallel to the superior surface of the temporal lobe. The current was off during insertion. Six volts, 60 cycles per second, 2.5 msec. duration, was applied at the tip of the electrode. The lips moved to the left and upwards, then puckered as the stimulus continued. The jaw moved downwards. All movements ceased with the cessation of stimulus. A brief afterdischarge was noted at electrode 5 close to point 4. There was no other electrographic abnormality. The patient described the movements (made during deep stimulation) accurately. He said he felt as if "someone else was doing it." He could not stop them.

During subsequent excision the depth electrode tip was located just above the anterior end of the temporal horn. Figure 4 illustrates the location of the significant stimulation points and the approximate location of the depth electrode. The facial movements are shown.

Case 3.—A 31 year old farmer has had cerebral seizures since the age of seven years. These were frequent despite intensive medication. Clinical, x-ray, and electrographic evidence localized their origin in the right temporal lobe. There was evidence of electrographic abnormality in the left temporal region as well. He was warned of an attack by a buzzing noise in both ears, followed by a series of familiar thoughts. He could always recall and describe the noise but never the thoughts. He stared, became pale, plucked at his clothing, and smacked his lips during an attack. His consciousness was altered immediately after the warning.

During right osteoplastic craniotomy stimulation was carried out at point 1 (6 volts, 60 cycles per second, 2.5 msec. duration). The patient said, "Something in my tongue – all over."

The depth electrode was inserted at point 7 parallel to the superior surface of the temporal lobe. At 3.5 cm. stimulation with 6 volts, 60 cycles per second, 2.5 msec. duration, was followed by a quick eversion of the right upper lip. This was repeated three times with the same result. The response was immediate, but it was not coincident with electrographic abnormality from the cortical electrodes. The location of the electrode tip was identified at the anterior end of the lateral horn during excision. Figure 5 illustrates this and the facial movements as well. The stimulation point diagram shows the position of point 7 on the surface.

Case 4.—A man of 43 had never been able to work because of daily cerebral seizures which began in the second year of life. These were localized in the right temporal lobe by clinical, pneumographic, and electrographic evidence. His attacks usually began with alteration of consciousness and were characterized by lip smacking and plucking movements of both hands.

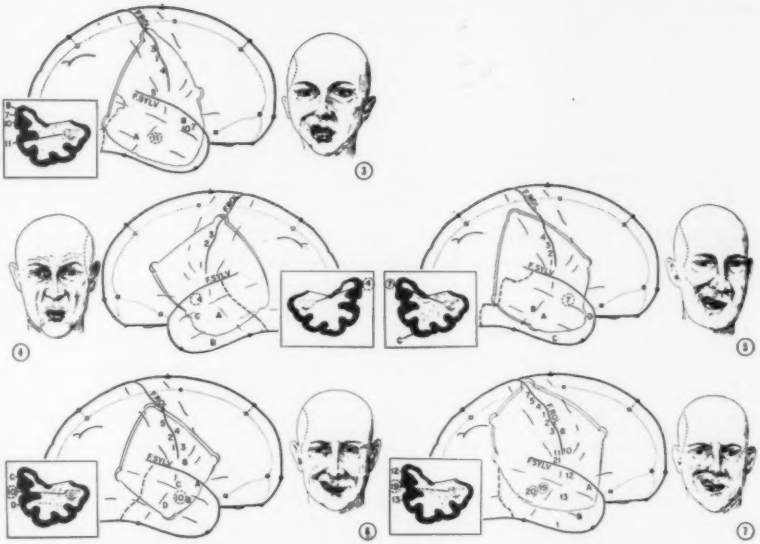


FIG. 3. *Case 1.* Illustrating the ipsilateral lip movement which followed stimulation at point 11.

FIG. 4. *Case 2.* Illustrating lip movement following deep stimulation through point 4.

FIG. 5. *Case 3.* Illustrating lip movement following deep stimulation through point 7.

FIG. 6. *Case 4.* Illustrating lip movement following deep stimulation through point 10.

FIG. 7. *Case 5.* Illustrating the lip movement following deep stimulation through points 19 and 20.

At operation the depth of the right temporal lobe was stimulated through the point marked 10. The depth electrode was directed downwards and mesially parallel to the superior surface for a distance of 2.5 cm. A current of 6 volts, 60 cycles per second, 2.5 msec. duration, was introduced. The patient said, "Smiling." A quick grimace was noted beginning and ending with stimulation. The right corner of the mouth pulled upwards. There was no coincident electrographic abnormality. The depth electrode tip was crudely localized as shown in figure 6, which also illustrates the facial movements and the stimulation points. Stimulation responses (3 volts, 60 cycles per second, 2.5 msec. duration): 8. "I felt like my throat was closing up somewhat and I could not talk." 3. "The left side of my cheek seemed like it was turning in and then pulled up."

Case 5.—A 22 year old university student had frequent cerebral seizures. These began five years previously and continued despite adequate medication. These were ushered in by an erotic sensation. This was followed by alteration of consciousness, lip smacking, and fumbling movements of both hands.

At operation, after exposure of the right temporal region, the surface of the brain was explored by electrical stimulation and recording electrodes. After stimulation with 4 volts, 60 cycles per second, 2.5 msec. duration, at point 21, the patient said, "A tingling inside my mouth."

The depth electrode was introduced in an anterior and mesial direction for a distance of 3.5 cm. from point 19. Stimulation at 4 volts, 60 cycles per second, 2.5 msec. duration,

produced gross movements of the tongue, and afterwards he said he could not stop them. The electrode was withdrawn and reinserted in a similar direction for the same distance from point 20. On stimulation with 4 volts, 60 cycles per second, 2.5 msec. duration, the patient said, "A twitching of the right side of my face." This was confirmed by the observer. It began and ended with the stimulating current. There was no clinical or electrographic evidence of seizure discharge. The stimulation points, direction of the depth electrode and the facial responses are summarized in figure 7.

In each of the preceding cases the depth of the mesial and inferior region of the temporal lobe has been stimulated in a conscious, alert patient. These deep stimulations were followed by movements of the face, jaws, and tongue. The facial movements occurred on the same side as the stimulus except in one case, in which the patient puckered his lips in a sucking movement. Ipsilateral facial movements consisted of eversion of the upper lip and wrinkling of the nasolabial fold. In one case the jaw began to "clench." In another the patient's jaw was thrust forward. In the last case the tongue protruded to the opposite side. All movements began promptly with the stimulus and ended abruptly as the current was turned off. In every case the patient remained conscious and alert during the period of the stimulations, and there was no clinical or electrographic evidence of seizure discharge.

In order to eliminate the various possibilities of current spread from the point of the electrode, we have stimulated the uncus and hippocampus with the same parameters, without apparent response. Similarly, we stimulated the dura over the ganglion and branches of the fifth nerve. A prompt pain response followed this stimulation and no movement of the jaw occurred. This was repeated at lower voltages (1 to 2 volts) and again evoked pain without movement.

Stimulation over the dura elsewhere in the middle fossa produced slight pain or no response. There was no movement. During the response to pain the patients occasionally grimaced. This was a quick bilateral movement of the corners of the mouth. It often persisted after stimulation ceased.

The lowermost portion of the somatosensory cortex, upper bank of the sylvian fissure, insula, and cerebral peduncle were also stimulated with 1 to 6 volts. No ipsilateral movements of the face were evoked, nor were there any jaw movements (although these have been evoked from the lowermost somatosensory areas).[4]

We have followed the electrode tip in its course towards the anterior end of the lateral horn in each case. This has been done with suction dissection and adequate visibility.

From a consideration of the operative anatomy and the principles of deep stimulation technic which have been described, we assume that the electrode tip lay in or very close to the amygdaloid nucleus in each case. This assumption is illustrated in figure 8.

Movements of this type may follow stimulation of the amygdaloid nucleus. The experimental evidence is clear. MacLean and Delgado,[5] Kaada and coworkers,[6] and others have investigated the amygdala with Horsley-Clarke

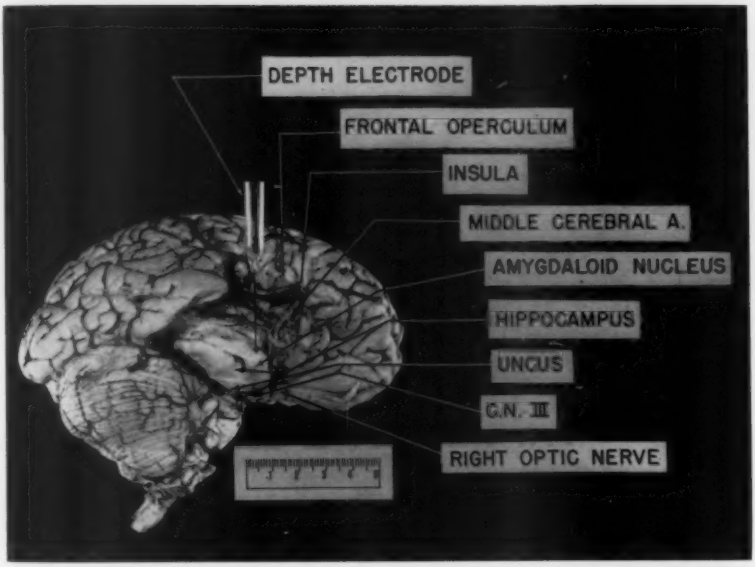


FIG. 8. A brain dissection illustrating the approximate position of the depth electrode tip in relation to the deep structures. This dissection also serves to illustrate the area exposed after the excision, which is essential in most of these cases.

technics and their detailed results include face and jaw movements as well as autonomic responses. The facial movements which they have evoked from this group of nuclei are usually ipsilateral with regard to the side of stimulus. Kaada emphasized that these movements of the face and jaws are most frequently derived from the mesial portions of the amygdala as compared to the responses from the lateral areas. The latter he related to complex behavioral changes.

David Ferrier,[7] in 1876, reported "torsion of the lip and semiclosure of the nostril on the same side" following "electrical irritation" on the anterior and inner aspect of the uncinate gyrus (subiculum cornu Ammonis). His illustration is reproduced in figure 9. He compared these facial movements to those which follow ipsilateral olfactory stimulation in the monkey.

The clinical evidence would seem to indicate that electrical stimulation deep within the sylvian fissure or beneath the temporal lobe is often followed by movements of lips, tongue, jaws, and occasionally swallowing and salivation. This has been the experience of Penfield and Jasper.[4]

Hughlings Jackson[8] called these gustatory movements and localized them by inference from the work of Ferrier which we have quoted.

Penfield and Kristiansen[9] stated that alteration of consciousness is the most frequent initial phenomenon of a seizure in which masticatory movements

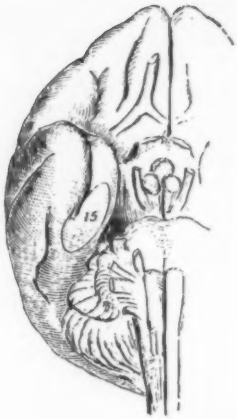


FIG. 9. David Ferrier's drawing of the area from which he evoked the lip movement which is described in the part of his test shown above.

occur. This is emphasized by Penfield and Jasper.[4] They suggested an origin for these movements in the region of the amygdala. In this regard Pribram, Lennox, and Dunsmore[10] and Pribram and MacLean[11] have shown that the entire frontotemporal region may fire into the amygdala and rostral hippocampus. Hence, one need not assume a focus of epileptiform discharge in the amygdala itself in order to insure its role in the production of facial and jaw movement. The discharge may spread to this structure from a primary focus elsewhere in the temporal lobe or adjacent frontal areas.

Obviously the movements which we have observed are only fragments of the gustatory and masticatory processes and they were not associated with any noticeable alteration of consciousness or other evidence of seizure discharge.

On the basis of the previous clear experimental evidence, as well as reasonable inference from clinical experience, we have tried to reproduce these movements by stimulations in the amygdala of the Macaca mulatta.

During these stimulations we have sought information concerning the ipsilateral or bilateral nature of these motor activities: specifically, whether movements on one side always followed stimulation of that side, or if movements which are at first ipsilateral to the stimulus may become bilateral.

Obviously, we are concerned here with the problem of functional connections between the temporal poles. Stoll, Marsan, and Jasper[12] have presented clear evidence for such physiologic relationships. It may be that these are actually functional relationships between the amygdalae.

TECHNIC AND METHODS

Observations were made in three acute and six chronic preparations. In each animal bipolar electrodes of stainless steel were directed towards the amygdala with the stereotaxic apparatus. These electrodes were secured to

the skull with an acrylic substance. This technic has been described by Bradley and Elkes.[13]

Both sides have been stimulated separately in each case. In two monkeys both sides were stimulated simultaneously. The three acute preparations provided opportunity for afterdischarge studies. They were stimulated on one side while recordings were made from the opposite depth electrodes. In these cases we have also recorded from various cortical areas during the deep stimulation by means of six pairs of electrodes. In the chronic preparations we have studied stimulation effects in both the conscious state and under anesthesia. The anesthesia was pentobarbital (0.5 cc./kg. body weight), which was given in order that discrete reactions might be observed. All made good recoveries from operation. These animals were stimulated on one or the other side while in an observation box. Their activities during stimulation were photographed in color.

All depth electrode positions have been confirmed by histologic study.

OBSERVATIONS

The histologic evidence for the location of the stimulating electrodes is summarized in figure 10. All placements were made within the amygdala

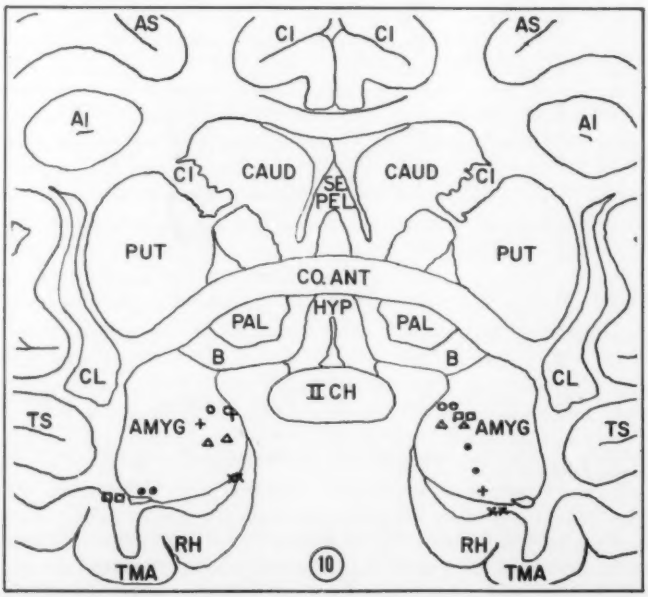


FIG. 10. Diagram of a histologic section of the monkey's brain in which the location of the electrode points are shown by symbols. The symbols may be identified in each case by referring to table 1.

TABLE 1

AN ANALYSIS OF THE STIMULATION RESPONSES OBTAINED FROM STIMULATION OF THE AMYGDALOID NUCLEI IN THE MACACA MULATTA

No.	Location of Lesion*	Side	Cons. or Anes.	Movements: Lip	Tongue	Jaw	Eye Lid	Head	Autonomic Reaction
2.	R: S-M	R	C	Yes		{Open Close	Close	Turn to Left	
	L: S-M	R	A				Open Blink slowly		Salivation—left eye tearing Resp. I.A.**
		L	A	Yes	To left and to midline several times	{Open Close	Open Blink slowly		Ipsi. pupil dilation Resp. I.A.**
3.	R: S-M	L	C	Yes			Close	Turn to Right	
	L: I-C	R	A						Cardiac rate increase 128 to 188 Resp. I.A.**
		L	A	Yes			Close		
4.	R: I-L to Amyg.	R	C	Yes			Close	To Left	
		L	C	Yes		Open	Close	To Right	
	L: S-M	R	A	Yes				To Left	
		L	A	Yes	To Left	Close	Close		
5.	R: M-C	L	C	Yes		{Open Close	Close		
	L: S-M	R	A			Close	Twitch		
		L	A	Twitch			Twitch		
6.	R: I-L	R	C	Yes	Lick on left	To left	Close	To Left	
	L: I-C	L	C	Yes	To left	{Open Close	Close		
		R	A			Close	Twitch		
		L	A			{Open Close	Twitch		
7.	R: M-C L: I-L To Amyg.	R	C	Yes	Yawn		Close	To Left	
		L	C					To Left	
		R	A	Yes		To right			Left eye tearing
		L	A			{Open Close	Twitch		Salivation

*Key: R: Right, L: Left, S-M: Superomesial, I-C: Inferocentral, I-L: Inferolateral, M-C: Mediocentral.
**Respiration: inspiratory arrest.

except one. Indeed, the majority of lesions which mark these placements are within the superomesial quadrant of the amygdaloid nucleus.

In each case the first and most frequent responses were movements of the lips, face, and jaws. These movements actually developed in a particular sequence. This began with eversion of the ipsilateral lip, quickly followed by

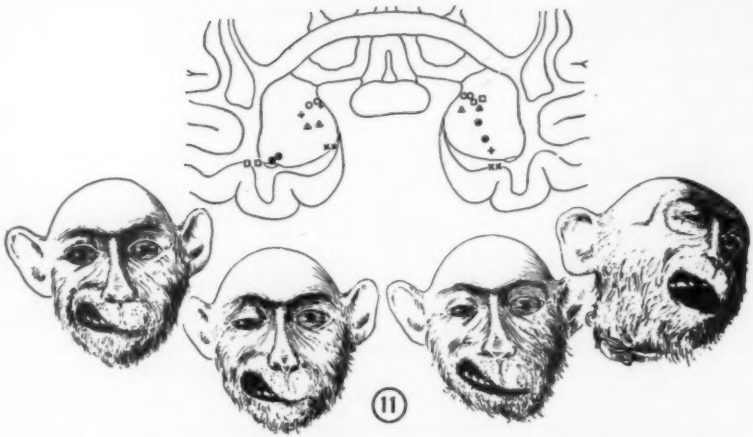


FIG. 11. The particular sequence of face and jaw movements followed by contralateral head turning which were evoked in the Macaca mulatta. The location of the stimulation points as confirmed by histologic study is also shown.

wrinkling of the nasolabial fold and closure of the ipsilateral eye. Next there were chewing movements, followed by turning of the head away from the side of stimulus. This sequence is illustrated in figure 11. It may be important that this sequence was most striking and began most promptly where the stimulating electrodes were most superior and mesial in the amygdala. In the chronic group we did not observe any particular behavioral or feeding idiosyncrasies in the intervals between stimulations.

All animals showed some autonomic responses. The most frequent were inspiratory arrest of respiration and tachycardia. Salivation also occurred. The detailed observations are summarized in table 1.

In one acute and one chronic preparation we stimulated the two amygdalae simultaneously (at 6 to 8 volts). This was promptly followed by a generalized seizure in each case.

In the acute preparations we stimulated the right amygdala with repetitive currents at 10 volts, 60 cycles per second and 2.5 msec. duration. Recording electrodes on the second and third convolutions of the right temporal lobe showed spikes. Then electrodes located along the lateral aspect of the left (opposite) amygdala began recording afterdischarge related to our repetitive stimulation on the right. This was not recorded from the second and third temporal convolutions on the left side, nor was it noted in tracings from electrodes on left frontoparietal or right occipital cortex. As the stimulus began in the right amygdala of these animals, ipsilateral facial movements commenced, followed by chewing and ipsilateral eyelid movement. When the afterdischarge was recorded from the opposite depth electrodes, the facial

movements became bilateral and chewing continued. This afterdischarge is illustrated in figure 12. It was obtained 25 times with similar corollary responses.

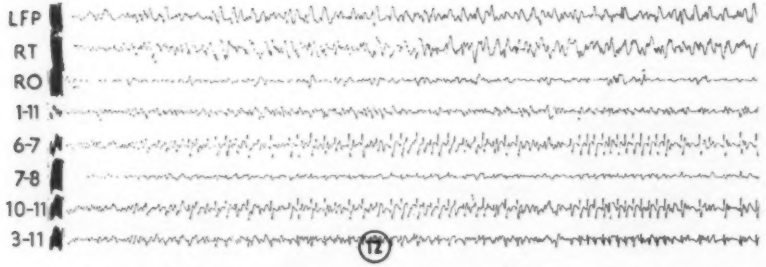


FIG. 12. The afterdischarge from the left amygdala following stimulation of the right amygdala is shown by a tracing at electrode pairs 6-7, 10-11, and 3-11. There were five pairs of electrodes in this area. Sample inkwriter tracings from left frontoparietal, right temporal, and right occipital are also shown. Stimulation artefact was also present.

If the voltage was increased from 10 to 15 (with 60 cycles per second and 2.5 msec. duration), an electrographic seizure could be recorded from the opposite depth electrodes. Actually, the first record of this electrographic attack was from the right temporal lobe. (We were not recording in the right amygdala.) This seizure then began and continued in the neighborhood of the left amygdala for 45 seconds before spreading to the cortical electrodes. The order of spread as recorded from the cortex of the opposite hemisphere was left temporal, left frontoparietal, left occipital, and then it became generalized. There were no movements during the electrographic seizures.

Once the afterdischarge had been established as a phenomenon which could be recorded with regularity, we cut the anterior commissure and the anterior corpus callosum in one animal. Following this incision we could not record the spread of afterdischarge to the opposite side (figure 13), although we did obtain ipsilateral facial movements as described previously.

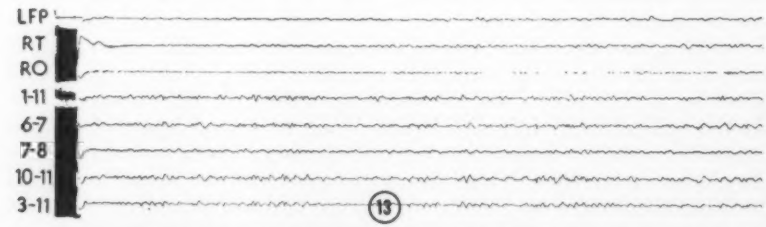


FIG. 13. Inkwriter tracings of the electrodes in the left amygdala are shown. These tracings do not demonstrate afterdischarge despite the fact that the right amygdala is being stimulated in the same manner as developed the afterdischarge shown in figure 12. The anterior commissure has been cut in this animal. Sample tracings from left frontoparietal, right temporal, and right occipital are also shown. Stimulation artefact was also present.

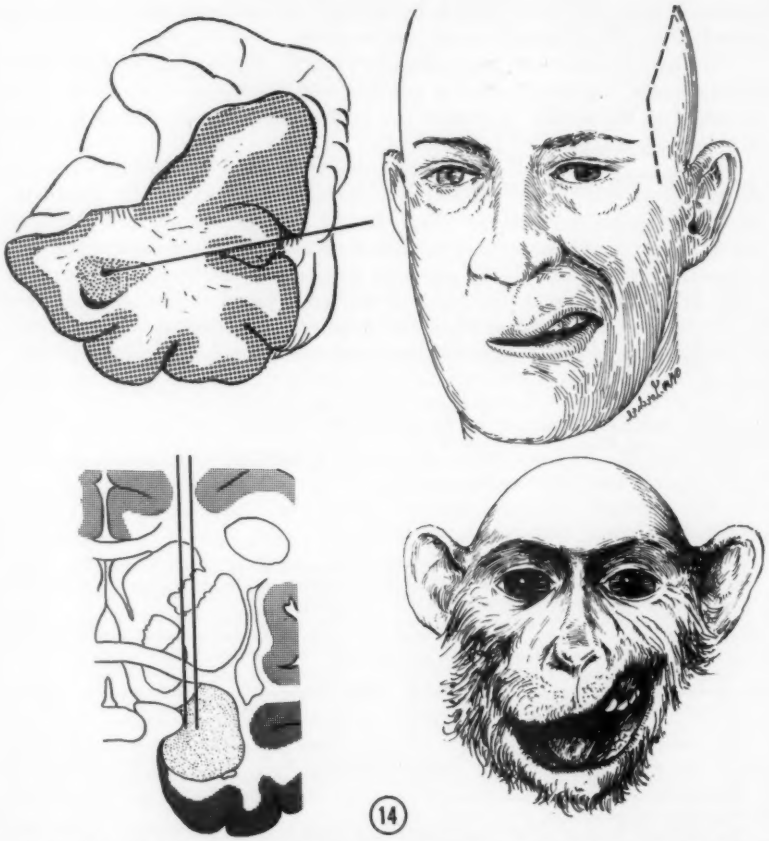


FIG. 14. Artist's conception of the ipsilateral movements of upper lip in the human and in Macaca mulatta. The approximate position of the stimulating electrodes in the human temporal lobe and the amygdala of the monkey are also shown.

DISCUSSION

From these preliminary observations we conclude that movements of face and jaw follow electrical stimulation of the mesial amygdala in the Macaca mulatta. The movements which we have observed follow a particular pattern. This begins with eversion of the upper lip on the same side as the stimulus. The movements of face become bilateral following repetitive stimulation of the amygdala on one side. Then an afterdischarge may be recorded in the region of the opposite amygdala. This suggests a functional connection between the amygdaloid nuclei, and it may be that we have interrupted the

structural basis of this connection by cutting the anterior commissure in one animal. These relationships await further study.

The movements of face and jaw which follow electrical stimulation of the inferior mesial temporal region in patients seem analogous to those we have described as the results of stimulation in the amygdala of Macaca mulatta. This analogy is illustrated in figure 14.

On the basis of this physiologic evidence we suggest that epileptiform discharge in one amygdaloid nucleus may spread rapidly across the midline to the other amygdaloid nucleus. Thus clinical and electrographic evidence of this discharge may appear on either side soon after its origin deep within one temporal lobe. Such discharge need not originate in the amygdaloid nucleus itself. It may arise in the temporal cortex and spread to the amygdala beneath. Pribram, Lennox, and Dunsmore[10] have demonstrated that epileptiform discharge arising in the temporal cortex may affect the ipsilateral amygdaloid nucleus.

These studies have been accomplished with the technical assistance of Miss Shirley Lewis, R.N., and Philip P. McGrath, B.A.

The Thalamus of the Macaca Mulatta, an atlas prepared by Dr. Jerzy Olszewski, has been used as the basic reference for stereotaxic and histologic studies.

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Clinical Differential Diagnosis of the Minor Seizure

Hal C. Gregg, M.D. and Augustus S. Rose, M.D.

IN THE PAST DECADE a new nosologic entity has been identified in the field of epileptology, namely, the psychomotor seizure.[1] Because of the realization that this type of seizure is probably the most common and because the pathologic physiology is complex and poorly understood, it was decided to investigate a group of known epileptics by means of careful historical, neurologic, and electroencephalographic examination. It became apparent that many patients suffered from very brief attacks. Commonly, however, these seizures were misdiagnosed and treated as petit mal epilepsy. Thus the differential diagnosis of the brief, minor seizure is one of the most important in the field of epilepsy. The purpose of this paper, then, is to present criteria by which the minor seizure may be differentiated.

MATERIAL

The survey group consisted of 100 patients all of whom were males except three, ranging in age from 22 to 67. Eighty-five of the patients were domiciliary patients of the Los Angeles Veterans Administration Medical Center, 12 were receiving hospital care at the Wadsworth General Hospital, Veterans Administration, and three were outpatients. Of the entire group, 71 per cent suffered from psychomotor seizures alone or in conjunction with grand mal episodes. Of the patients with psychomotor seizures, 82 per cent reported some sort of brief, minor attack. While an incidence of 71 per cent of psychomotor seizures may appear high, it is not inconsistent with other reports nor with the type of patient examined.[1] It must be remembered that all of the domiciliary patients are incapacitated socially and economically primarily because of the nature of their seizures.

Domiciliary patients provide a unique opportunity for careful investigation. Because they lead a semi-military life, they are readily available for interview allowing meticulous, repeated historical examinations to be carried

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out. Personality and behavior aberrations are officially reported. There are many witnesses for every attack, so that ictal behavior may be ascertained in detail. But above all the examiner learns to know each patient intimately as a person. Because of these circumstances it is believed that the clinical observations made of psychomotor epilepsy, and particularly of the minor seizure, are sound.

Eighty-eight patients were examined electroencephalographically. The remaining number could not be examined because of intervening illness, death, or transfer to other facilities. Examination was done on a type D-3 Offner machine, using 18 electrodes and both monopolar and bipolar recordings. Of the patients examined 87 per cent had abnormal records. Seventy-six per cent of the abnormal records showed some focal abnormality of the temporal lobes, such as spiking, slowing, or asymmetry. Portions of the records from the two cases cited below represent the type of temporal lobe abnormality typically seen (figure 1).

ILLUSTRATIVE CASES

Two cases are presented as examples of patients with brief seizures. Both of these patients had been previously diagnosed and treated as petit mal epilepsy.

Case 1.—A 30 year old man stated that in October 1944 he was blown out of a fox hole by an 88 mm. projectile. He suffered multiple flesh wounds and was dazed for 15 minutes, but received no direct injury to the head. Three months later, in January 1945, he began to have episodes of dizziness lasting two or three minutes and occurring several times a month, usually accompanied by a sensation of nausea arising from the epigastrium. Although he did not lose consciousness, a minute or two passed before he was himself again.

Two years later, in May 1947, he suffered his first grand mal seizure, characterized by tonic and clonic movements as well as tongue biting. They have continued until the present at the rate of one a month. No aura has ever preceded this type of seizure.

On direct questioning it was learned that for approximately one year prior to the first grand mal episode he had begun to have brief episodes in which he suddenly lost the ability to speak and to understand, and in which he lost consciousness for a moment. This type of attack has always been preceded by a peculiar, especially vivid, thought in which the patient suddenly thinks of someone, place, or object he knew many years ago. The patient was unaware of the loss of consciousness. His wife revealed this and, in addition, stated that he always smacked his lips loudly and rhythmically with each episode. Immediately following the attack he is vague and confused for several minutes. This type of seizure has occurred as frequently as two or three times a day.

Case 2.—A 37 year old man began in 1947 to have episodes lasting a second or two in which he felt as though he were going to faint but did not lose consciousness. In 1948 the frequency increased and his wife began to note that he would suddenly stare and smack his lips for a few minutes. Since 1948 the attacks have increased in frequency to 15 a month. At the present time the attack consists of a brief aura in which he feels as though he is going to "pass out," immediately following which he loses consciousness. His wife reports that he stares vacantly, smacks his lips loudly for a few seconds, and may stiffen generally. In a moment following the tonic movements, he usually mumbles incoherently and then begins to speak normally within a few minutes. Five minutes after onset he is mentally clear.

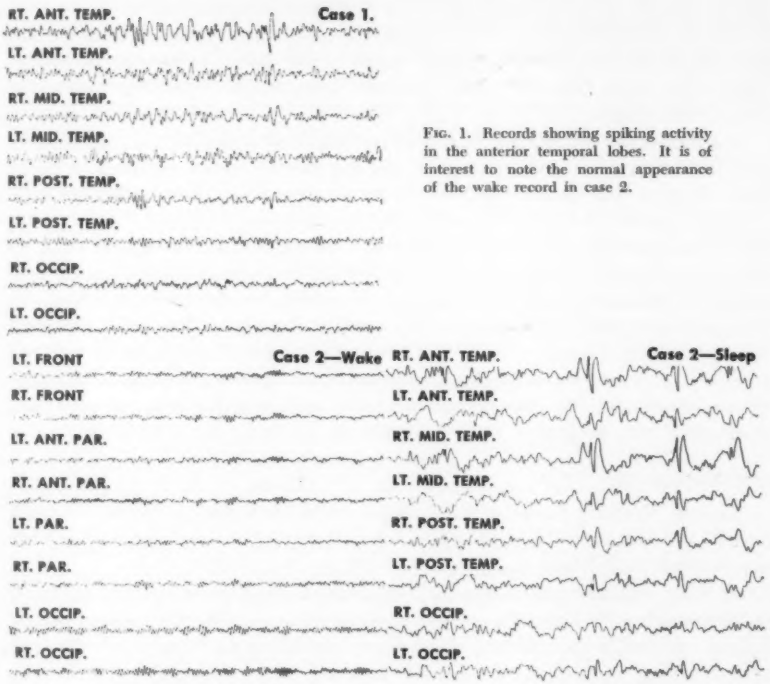

FIG. 1. Records showing spiking activity in the anterior temporal lobes. It is of interest to note the normal appearance of the wake record in case 2.

COMMENT

There are several points to be made from such a study: 1) the frequency with which the brief attack occurs as a manifestation of psychomotor epilepsy, 2) the frequency with which the minor episode is either ignored or misdiagnosed as petit mal, 3) the necessity of asking the patient directly about the brief attacks, 4) the necessity of reassuring the patient that brief, bizarre episodes are well known and do not indicate insanity.

Brief episodes are frequently ignored because both patient and physician focus their attention on the awesome grand mal seizures. When this type of seizure is brought under control, both are usually content to allow a "few little ones," not realizing that it is from the minor discharge that the general, cerebral storm may occur. Brief episodes are frequently misdiagnosed because by tradition the term petit mal is used to describe the severity of a seizure in a roughly quantitative way.[2]

It is essential to ask the patient directly about the brief seizure. They will rarely volunteer such information, not only because they are willing to accept brief seizures in the face of grand mal, but also because they believe the brief,

bizarre episode will be misconstrued as psychotic behavior and that they may well be confined therefore. It is imperative to explain in detail to each patient that for diagnostic and therapeutic purposes the minor seizure is as important as the large, that what they "confess" is an actual experience and not a break with reality.

Because only one patient in the series had petit mal epilepsy, the distinction between psychomotor and petit mal automatism did not become a problem. Penfield and Jasper, however, state that petit mal automatism may be clinically indistinguishable from the psychomotor automatism.[3] Only careful electroencephalographic studies will differentiate, and even then it must be remembered that a certain portion of psychomotor seizures show bilateral synchronous discharges with little firing to the surface in the temporal areas. In such instances one should question the patient directly to determine the presence of any type of aura. Those who have witnessed a seizure must be quizzed carefully to discover every detail of the patient's behavior, especially the type of movement and the presence of postictal confusion, for even in petit mal automatism the patient is clear immediately following the attack.[3]

DIFFERENTIAL DIAGNOSIS

Lennox classifies the petit mal epilepsies into three distinct types: 1) petit mal, 2) myoclonic, and 3) akinetic.[2] A fourth type, petit mal automatism, has been added by Penfield and Jasper.[3]

1. Petit mal epilepsy, primarily a disease of children, consists of brief (5 to 30 seconds), frequent lapses of consciousness. Usually the patient is immobile, muscular movements, if any, are restricted to regular, rhythmical, clonic jerking, usually at the rate of three per second involving the eyelids or brows, rarely the head and arms. They begin and end suddenly without aura or postictal phase. Mentality and personality remain intact in spite of thousands of attacks.[2]

2. Myoclonic epilepsy is characterized by single contractions of the flexor muscles of one or both limbs, occasionally of the trunk musculature. There is no loss of consciousness.[2]

3. Akinetic epilepsy, rarely occurring in adults, consists of a sudden loss of postural control. Without warning or muscular movement the child collapses. Usually the patient rises immediately but may lie for several minutes. Almost never is there alteration of consciousness. Except for the lack of an emotional excitant, the episode may well resemble cataleptic attacks.[2]

4. Petit mal automatism occurs only rarely. This type of attack may be clinically indistinguishable from one of temporal lobe origin. For example, there may be lip smacking, fumbling movements of the hands, and wandering about in a confused manner.[3]

In an excellent monograph read before the National League Against Epilepsy in 1953, Gastaut presented a clinical analysis of the ictal symptomatology. He grouped the symptoms broadly into three categories: 1) sensory and sen-

sorial, 2) mental, and 3) motor, each of these broad categories having a multitude of manifestations.[1] What must be emphasized is that these signs and symptoms, occurring in any one of the categories, may be very brief and thus confused with a petit mal seizure.

The following diagnostic criteria are offered in order to facilitate the clinical differential diagnosis of the minor seizure.

1. *Age:* Petit mal epilepsy is a malady of young people. It does not begin after the age of 20.[2] While psychomotor epilepsy may occur at any age, it is primarily a condition of adults. If the seizure has begun after the second decade, the possibility of petit mal epilepsy is essentially ruled out, and the brief episode is in all probability psychomotor.

2. *History:* It is chiefly by careful history taking that the proper diagnosis is made. Patients are hesitant to discuss bizarre episodes because it is feared that the story will be misinterpreted as a true break with reality. Frequently the minor seizure can be detected only by direct questioning.

3. *Personality:* Psychiatric symptomatology is relatively uncommon in petit mal epilepsy.[2,4] In contrast, psychiatric symptomatology in psychomotor is common and not infrequently incapacitating.[1,4] The so-called "epileptic personality" may be the personality of those who suffer from psychomotor epilepsy.[4]

The psychomotor epileptic often presents a management problem, therapeutically, economically, and socially. He is generally hostile, quick to project and then seek revenge against authority. Rarely does he have a good work record, losing positions as much through emotional instability as seizures. At the same time, he is eager to gain attention; the slightest change in seizure pattern or even general well being is immediately and officiously reported. Maritally he does poorly. Often he is in some sort of trouble.

It should be noted, however, that there are instances in which the interictal personality is pleasant. For example, Case 1 is an exceptionally intelligent, cooperative, pleasant man whom it is a pleasure to treat. Interestingly enough, as Gastaut has pointed out, the waking interseizure electroencephalogram is entirely within normal limits. In contrast, Case 2 has much psychiatric symptomatology and has a generally as well as focally dysrhythmic interictal record.

4. *Ictus:* The presence of an aura is an important differential point because it almost never occurs in petit mal, but is frequently present in psychomotor seizures. Usually the duration of the petit mal episode is shorter than the psychomotor. For the most part the patient with the petit mal seizure is immobile. Muscular movements are confined to rhythmic jerking or twitching at the rate of three per second, usually of the eyelids, brows, and rarely of the head and arms. Movements in psychomotor seizures in contrast are usually semipurposeful, involving the limbs individually. Wandering about and gustatory movements are common. Jargon or grunting sounds are common during a psychomotor seizure and almost never occur in petit mal. There is rarely

incontinence of bowel or bladder in petit mal. Incontinence is not infrequent in psychomotor seizures.

5. *Postictus:* The postictal phase is probably the most important and reliable means of differentiation. The patient with petit mal epilepsy is instantly clear following an attack. There is no mental clouding of any sort.[2,3] On the contrary, following a psychomotor seizure the patient is invariably confused. It must be emphasized that patients frequently state that they are mentally clear at once following an attack, but if questioned directly "at once" is actually a minute or two. If there is any postictal confusion or vagueness, no matter how minimal, transient, or brief, one can be certain a psychomotor episode has occurred.

6. *Electroencephalography:* The importance of careful electroencephalography, both waking and sleep records, is well known in the diagnosis of epilepsy.[5] In differentiating the minor seizures, however, it becomes especially important. It provides tangible proof of the clinical suspicion.

CONCLUSIONS

1. One hundred known epileptics were studied. Of these 71 per cent have psychomotor seizures either alone or in conjunction with grand mal episodes.

2. Eighty-two per cent of the patients with psychomotor epilepsy have some sort of brief, minor seizures.

3. Brief seizures are frequently misdiagnosed as petit mal. Diagnostic criteria for the differential diagnosis of the minor seizure are offered.

The authors are indebted to Mr. J. H. Thomson for his technical assistance in electroencephalography.

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Collateral Ophthalmic Artery Circulation in Thrombotic Carotid Occlusion

Kjeld Vaernet, M.D.

THE EXISTENCE of anastomotic connections between the external and internal carotid arteries by way of the ophthalmic artery is common knowledge. The significance of this collateral circulation is well known to neurosurgeons, particularly in cases of arteriovenous aneurysm of the cavernous sinus. In such cases it may be the main factor in maintaining the blood supply of the aneurysm after carotid ligation.[1,2] In cases of occluding vascular lesion of the internal carotid, a collateral circulation to ensure sufficient blood flow to the corresponding hemisphere will be established primarily as a basal collateral circulation by way of the anterior and posterior communicating arteries.[3,4] There is evidence, however, that the ophthalmic artery must also be regarded as a potentially important collateral pathway in these cases. Marx[5] reported one case of unilateral and one of bilateral thrombosis of the internal carotid. The angiogram in both cases showed filling of the distal part of the carotid syphon and the large vessels of the Sylvian group via the ophthalmic artery. The latter was seen anastomosing with the anterior branch of the middle meningeal artery. Krayenbühl and Richter[4] reported two cases of thrombosis of the internal carotid. In the carotid angiograms contrast medium was seen in the intracranial vessels only in the basilar artery and its branches. The influx occurred through anastomotic communications from muscular branches of the occipital artery (from the external carotid) to muscular branches of the vertebral artery in the neck. Cases are rare in which it has been possible to demonstrate by angiograms such functionally significant anastomoses between the extracranial and the intracranial arterial systems. Consequently it seems justified to report some further cases.

CASE REPORTS

Case 1.—A 48 year old man experienced a sudden cold sensation in the right leg nine months before admission. After a few days this was accompanied by persistent tingling and numbness in the leg. Three to four months before admission these symptoms were

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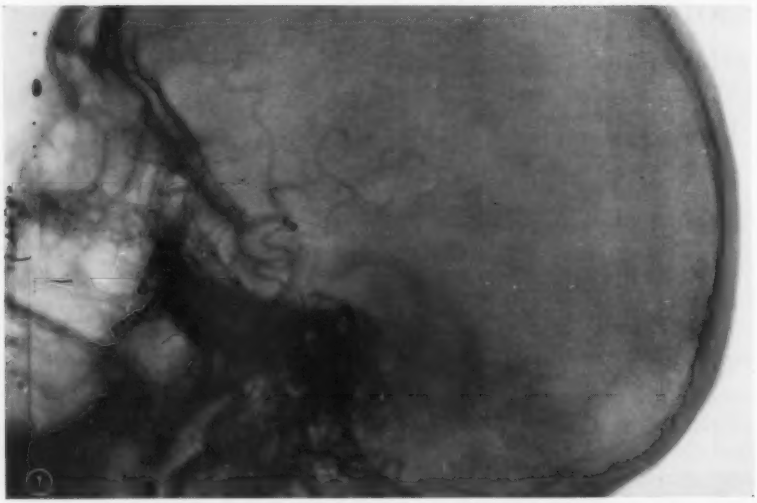

FIG. 1. *Case 1.* No filling of the internal carotid in the neck. Filling of the peripheral part of the carotid syphon and the middle cerebral vessels from the external carotid system, via the dilated ophthalmic artery.

more marked, and coincided with a feeling of weakness and awkwardness in the leg, associated at times with a sensation that the leg was not a part of him. All symptoms were more marked when walking, and occasionally they were associated with tingling in the right side of the trunk. The patient also noticed exaggeration of symptoms when smoking (he was not a heavy smoker) and on mental stress, particularly when he became agitated. During the last months he had become somewhat unstable emotionally, with a depressive tendency, irritability, and loss of memory for recent events.

Examination: Mentally the patient was mildly depressed. There was a mild aphasia, chiefly in the nature of dyslexia and dysgraphia, and a moderate impairment of retention and recall. Two-point discrimination and appreciation of number writing were impaired on the right leg, but normal on the right arm; stereognosis was normal. Otherwise no neurologic abnormalities could be discovered. The ophthalmologic examination was normal. Roentgenograms of the skull showed small calcifications in the wall of the right carotid syphon. Roentgenograms of lumbar spine were normal. The electroencephalogram showed slight dysrhythmia, but no focal abnormalities. Spinal fluid pressure was normal as was the protein content. The blood Wassermann was negative and blood pressure was normal. Oscillometric examination was normal. Skin temperature was normal on the legs. No dystrophic changes of the extremities were noted. Pneumencephalography (performed elsewhere four months before) showed mild dilatation of left lateral ventricle with no displacement.

Angiograms were made after injection into the left common carotid artery. The films showed maximal filling of the external carotid and its branches. Despite repeated injections there was no filling of the internal carotid in the neck or its intracranial portion central to the ophthalmic artery. Peripheral to this point there was a definite filling of the syphon and the main branches of the middle cerebral artery. There was no filling of the anterior cerebral artery. The ophthalmic artery was abnormally wide and could be followed in its entire course to its terminal branches. Distinct anastomoses were seen between these ar-

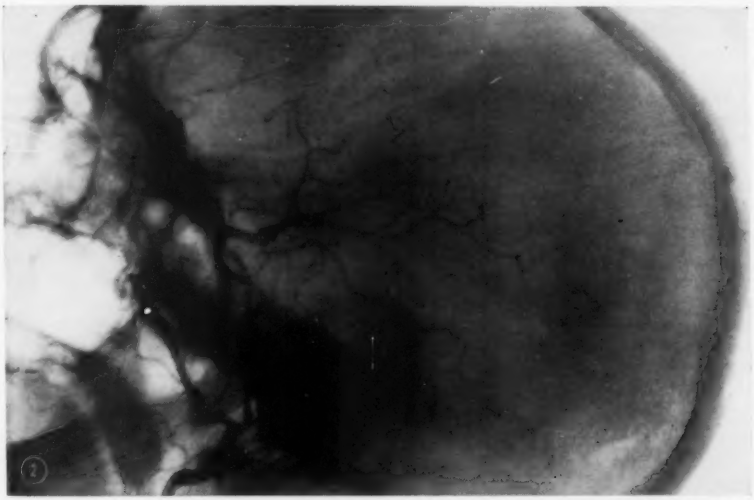

FIG. 2. *Case 2.* No contrast medium in the extracranial portion of the internal carotid. Carotid syphon and middle cerebral arteries are well visualized. The influx occurs from facial branches of the external carotid through the ophthalmic artery.

teries on the one hand and the infraorbital artery and branches of the facial artery on the other (figure 1). When exposed at operation the left internal carotid was found to be a firm cord into which injection was impossible and did not bleed on puncture. The common and external carotids were normal. Injection into the common carotid disclosed complete obstruction of the internal carotid about 1 cm. above the carotid bifurcation. Right-sided carotid angiography showed rather marked atheromatous changes of the carotid syphon; the course and ramifications of the right anterior and middle cerebral arteries were normal. In the anteroposterior view both anterior cerebral arteries and the left middle cerebral artery were seen filled from the right internal carotid.

Case 2.—A 49 year old man had developed a marked loss of memory for past and recent events about two years before admission. In the course of a few days this was followed by a gradual general mental deterioration with loss of initiative and attention, emotional instability, and marked fatigability. Intermittently he had episodes of paresthesias in the right extremities, accompanied by slight aphasic disturbances lasting from hours to days. Three weeks before admission he suddenly developed right hemiplegia and severe aphasia, with only slight improvement since then. On admission he was found to be sluggish and disoriented as to time and place, with profound mental reduction and moderate central aphasia involving all elements. He also showed emotional instability, frequently with uncontrolled weeping; slight right lower facial weakness; right spastic hemiplegia more pronounced in the arm; and a right Babinski response. There were no gross sensory abnormalities. Ophthalmologic examinations showed moderate sclerotic changes in the vessels of the eyegrounds; the field of vision could not be evaluated. Roentgenograms of the skull were normal. Blood pressure was 190/115. The spinal fluid was clear with normal cell count and protein content. The Wassermann test was negative for blood and spinal fluid.

Left-sided percutaneous carotid angiography disclosed complete absence of filling in the internal carotid artery in the neck and intracranially central to the sella. The peripheral part of the syphon and both the Sylvian group of vessels and the anterior cerebral

artery were well visualized. The vessels were rather narrow and their course normal. The ophthalmic artery was dilated, however, and was seen anastomosing with the facial branches of the well filled external carotid system (figure 2). The filling of the peripheral part of the syphon and the intracranial vessels from the branches of the external carotid artery via the ophthalmic artery could be demonstrated both in the lateral and in the anteroposterior view. Right-sided carotid angiography showed maximal filling of the internal carotid artery. Marked atheromatous changes were seen in the right carotid syphon. In the anteroposterior view there was maximal filling of the left anterior cerebral artery through the anterior communicating artery, with a beginning reflux into the horizontal part of the left anterior cerebral artery. Ventriculography showed moderate diffuse dilatation of the entire ventricular system, more marked on the left side, with no displacement.

Case 3.—A 52 year old woman with arterial hypertension developed a right-sided hemiplegia and aphasia without loss of consciousness during a few hours on the day of admission. On admission she was severely aphasic, could say only "yes" and "no," most often inadequately, and could not cooperate. She showed a severe right-sided, slightly spastic hemiplegia including the lower face, a right-sided Babinski response, but apparently no sensory changes. Ophthalmologic examination showed slight sclerotic and hypertensive changes of the vessels of the eyegrounds; the field of vision could not be evaluated. Otologic examination showed a normal reaction on caloric stimulation. The electroencephalogram showed nonfocal marked dysrhythmia, more pronounced over the left hemisphere. Roentgenograms of the skull were normal. The spinal fluid was colorless, with normal pressure and normal protein content. Blood pressure was 190/110. The blood Wassermann reaction was negative.

Bilateral carotid angiography with percutaneous injection into the common carotid artery disclosed, on the left side, a complete obstruction of the internal carotid artery which was only filled for about 1 cm. above the carotid bifurcation in the neck. No contrast medium was seen in the intracranial vessels, even after repeated injections and delayed exposures. There was maximal filling of the external carotid and its branches. On the right side there were marked atheromatous changes of the syphon and the intracranial vessels. The course and ramifications of the latter were normal. There was a slight filling of the left anterior cerebral artery through the anterior communicating artery, with a beginning reflux through the horizontal part of the left anterior cerebral artery.

On readmission three months later the patient's condition was essentially unchanged. Bilateral percutaneous carotid angiography now disclosed a definite filling of the peripheral part of the left carotid syphon and a few of the arteries of the Sylvian group. These vessels were markedly attenuated. Filling occurred through the slightly dilated ophthalmic artery, via anastomatic connections between the former artery and the branches of the left external carotid artery (figure 3). The left internal carotid artery was seen occluded above the carotid bifurcation as in the previous angiograms. On the right side a definite progression was noted in the atheromatous changes of the branches of the internal carotid artery with deterioration of the vascular supply to the right hemisphere. Especially there was complete absence of filling of the posterior temporal artery.

Case 4.—A 61 year old man had a slight and transient loss of motor power in the right extremities seven days before admission. Two days later he suddenly developed a severe right-sided hemiplegia and became totally aphasic. The symptoms were permanent thereafter. On admission he was found to be slightly somnolent with a total aphasia. He showed right-sided hemiparalysis including the lower face; marked spasticity in the right leg, slight in the right arm; right-sided hemihypalgesia including the face; and a right-sided Babinski response. Ophthalmologic examination was normal except that the fields of vision could not be evaluated. There were normal vestibular reactions on calorization. The spinal fluid was clear with normal pressure, cell count, and protein content. The electroencephalogram showed severe dysrhythmia and slow waves present diffusely. Roentgenograms of the skull were normal. The blood Wassermann was negative. Blood pressure was 150/100.

FIG. 3. *Case 3.* Filling of the carotid syphon and a few of the markedly attenuated middle cerebral arteries through the ophthalmic artery. The latter artery is anastomosing with the facial branches of the external carotid artery. Occlusion of the internal carotid artery in the neck.

Left-sided carotid angiography with percutaneous injection into the common carotid artery disclosed no filling of the internal carotid artery in the neck beyond a point 1 cm. distal to the carotid bifurcation. The external carotid artery and its branches were well visualized. Intracranially there was a slight filling of the distal part of the carotid syphon and in a few of the middle cerebral branches, which appeared markedly attenuated. The ophthalmic artery was well filled and was seen anastomosing with the terminal branches of the facial artery. The quality, however, of the aniograms was so unsatisfactory as to make the pictures unsuitable for reproduction. The vascular pattern was however essentially identical to that seen in figure 3.

In the right carotid angiograms severe atherosclerotic changes were seen in the carotid syphon and in the cerebral vessels. The branches of the middle cerebral artery were few and narrow. Both anterior cerebral arteries were filled from the right side, but no influx of the contrast medium was seen into the horizontal part of the left anterior cerebral artery. There was a marked delay in the rate of circulation through the branches of the internal carotid artery as related to those of the external carotid artery.

DISCUSSION

In case 1 an adequate collateral circulation to the left hemisphere seems to have been established, not only from the opposite side through the anterior communicating artery (as disclosed in the right angiogram), but also from the arteries of the same side as that of the thrombosis, namely through the ophthalmic artery. This artery seems to supply a sizeable amount of blood to the area of the middle cerebral artery. In this respect the case differs from the majority of cases of thrombosis of the internal carotid artery. In such cases the territory of the middle cerebral artery is usually in a less favorable posi-

tion than that of the anterior, as the territory of the anterior cerebral is more immediately supplied by collateral circulation and is of lesser extent, as pointed out by Ethelberg.[3]

Nothing can be concluded about the significance of the posterior communicating artery to the final result of collateral circulation in these cases since vertebral angiography has not been performed, but the anterior part of the circle of Willis appears to be more dependable than the posterior as a source of collateral circulation.[6] This is another point to the disadvantage of the middle cerebral artery regarding the establishment of a sufficient collateral circulation. This probably accounts for the common experience that hemiplegia in cases of carotid thrombosis, when not complete, is usually more severe in the arm than in the leg. This is seen in case 2.

In case 1 the well developed collateral circulation and the slight neurologic symptoms and findings suggest that the occlusion of the internal carotid has been gradual, probably secondary to an atheromatous process, as evidenced by the atheromatous changes in the right carotid syphon in the angiogram and the calcium deposits in its walls discernible in the radiogram.

In case 2 the history of recurrent and transient episodes finally leading to a severe and permanent hemiplegia (and aphasia) represent another of the main types in the course and evolution of carotid thrombosis. Here, as in the majority of these cases, the basic disease is an atherosclerosis of the carotid artery and the cerebral vessels, finally leading to occlusion of the carotid.

The onset of the acute episodes, transient or permanent, may be due to incidental causes, resulting in transient failing of a circulation already impeded by atheromatous changes of the vessels. Not only may a sudden onset of occlusion, even when affecting a minor cerebral vessel, deprive the brain of its blood supply in the territory of that vessel, but by eliciting widespread vascular spasm of long standing, it may also result in a varying degree of ischemia of extensive parts of the cerebral hemisphere for an appreciable period of time.[7] This phenomenon may account for the seeming inconsistency of the severe and permanent symptoms as related to the conspicuous collateral circulation as established in case 2.

Cases 3 and 4 were patients with marked atherosclerotic changes of the cerebral vessels, both representing an apoplectic onset of severe symptoms and a clearly inadequate collateral circulation. A discussion of the genesis of the various clinical symptoms and syndromes in cases of thrombosis of the internal carotid artery is outside the scope of this paper. However, there is no reason to resort to the more or less subtle explanations which have been put forward in great number and which are summarized by Elwidge and Werner.[8] The symptoms in each case are readily explained as depending on the adequacy (in time and volume) of the established collateral circulation. This will depend primarily on the general state of the vessels in the affected cerebral hemisphere, that is, in most cases the degree of atheromatous changes in these vessels. The pathologic changes may be different in the various arterial branches, thus accounting for the great variability in symptoms.

Probably a collateral circulation through the ophthalmic artery could be demonstrated in most cases of thrombosis of the internal carotid artery, especially if seriographic exposures were commonly employed in cerebral angiography. This collateral pathway probably accounts for most of the instances where contrast is seen in the syphon and cerebral vessels despite occlusion of the internal carotid in the neck. Apparently it also accounts for the angiographic pattern obtained in case 5 described by Elwidge and Werner.[8]

In cases of thrombosis of the internal carotid artery, ligation of the external carotid has been advocated, eliciting the middle meningeal reflex of Schneider in order to increase collateral circulation to the brain. But the fact that the ophthalmic artery can be an additional and hardly negligible source of supply would seem, however, to emphasize restraint towards this debatable procedure, as has already been pointed out by Marx.[5]

SUMMARY

Four cases of thrombosis of the internal carotid artery in the neck are reported. Filling in the angiograms of the carotid syphon and the intracranial vessels is demonstrated. The influx occurred via the ophthalmic artery through anastomotic connections between the terminal branches of this vessel and the external carotid system. The physiopathologic aspects of the collateral circulation in the brain is mentioned briefly, and the importance to cerebral circulation of the ophthalmic artery as an additional collateral pathway is stressed.

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Stimulation of "Second" Motor Areas in the Macaque Temporal Lobe

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CONTRACTION OF THE MUSCLES of the face on the side of stimulation and ipsilateral or bilateral movements of the upper and, occasionally, of the lower extremities have been elicited repeatedly on stimulation of the tip of the temporal lobe, the anterior portion of the superior temporal gyrus, and the lateral and basal portions of the inferior temporal gyrus. This is a preliminary report of the movements elicited. The interesting responses which were demonstrated suggest that considerably more attention must be devoted to discovering the pathways involved in the reactions. The results obtained from ablation studies in these animals and further stimulation experiments will be reported at a later date.

Ipsilateral movements on stimulation of regions of the cerebral cortex other than area 4 have been reported in various animals by numerous observers, including Wertheimer and Lepage,[13] Hering,[7] Rothmann,[11] Vogt,[12] Bucy,[1] Bucy and Fulton,[2] Wyss,[14] Lemmen,[9] and Lauer.[8] The ipsilateral representation of the extremities has also been demonstrated or suggested in human subjects by Foerster,[5] Gardner,[6] Dandy,[3] and Penfield.[10] Penfield and his associates regarded the regions from which these movements are obtained as "additional" motor areas. None of these reported ipsilateral responses upon stimulation of the temporal cortex of animals or man.

For an excellent discussion of ipsilateral movements, the reader is referred to the paper by Bucy and Fulton.[2] They were able to produce ipsilateral movements in monkeys by stimulating a restricted region about the superior precentral sulcus, predominately in area 6 but also including the anterior portion of area 4. They found that the responses were independent of the contralateral movements with which they were frequently associated and seemed to be carried by an ipsilateral tract through the central nervous system, although a double decussation within the brainstem could not be excluded.

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In their experiments the ipsilateral movement generally involved the lower extremity and consisted of sustained extension at all joints. However, this response was always associated with complex movements of the contralateral extremity which were ordinarily opposite in type, that is, exhibiting flexion at all joints rather than extension. More rarely responses were just reversed, extension instead of flexion was obtained in the contralateral limb, but in either case apparently they were never solely ipsilateral.

EXPERIMENTAL DATA

All studies were performed on four monkeys. In three of them craniotomies were carried out bilaterally, with periods of a week or two intervening, so that actually a total of seven separate operations was performed on these animals. Variations in cortical stimulation and ablation were employed to determine the effects of interrelationships of cortical areas on the evoked responses. The number of procedures is not great, but the responses were so specific in each instance that a preliminary report on the findings is indicated.

In all operations light, open-drop ether anesthesia was used. The frontotemporal cortex was exposed, with special effort directed toward an extensive unroofing of the tip of the temporal lobe. In the first two procedures, the animal was operated upon in the prone position with the head extended. In the remaining cases, however, it was found that exposure was facilitated by placing the monkey in the supine position with the face turned upward so that gravity caused the frontal and temporal lobes to fall backward, thus requiring less retraction of the temporal lobe and minimal pressure upon it. Stimulation of certain areas of the cortex was performed and the results recorded; selected areas were ablated; then, in most instances, restimulation was carried out to check for complete removal of the desired area. The wounds were closed, the behavior of the animals carefully observed, and after a given period the animals were sacrificed. The brains were photographed, sectioned, and prepared by the Marchi staining technic. There were no wound infections and all animals remained in good health throughout the studies.

All photographs in the following protocols were made with the brain tilted at a slight angle, so that the tip of the involved temporal lobe and the base of the brain could be visualized more readily.

In the accompanying plates the following symbols are used to illustrate the responses obtained from varying stimuli. The plain letter indicates an ipsilateral response; the prime (′) mark shows that a contralateral movement was obtained. The results may be indicated by combinations of letters, for example: F a′ l′, ipsilateral face with contralateral arm and leg.

F – Face	f – Forearm	m – Mouth	t – Toes
e – Eyelid	a – Arm	n – Neck	l – Leg
d – Horizontal deviation of eyes	s – Shoulder	h – Hand	

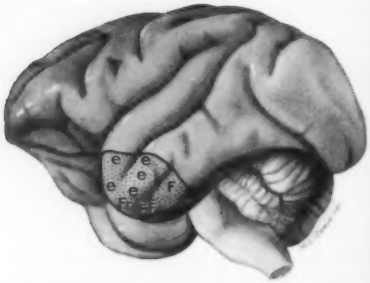


PLATE 1. Drawing of the macaque brain showing the regions of the left hemisphere from which movements were elicited on stimulation in monkey No. 1. For interpretation of legends, see protocol No. 1.

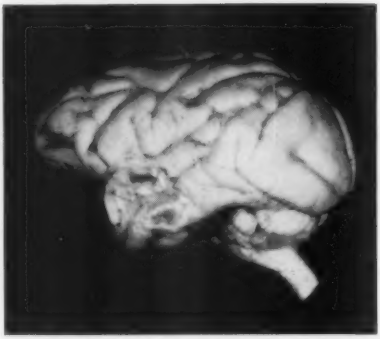


FIG. 1. Site of cortical excision of anterior left temporal lobe.

PROTOCOLS

Protocol No. 1 – Monkey No. 1 (Macaca mulatta)

On April 20, 1951, a left temporal craniotomy was performed, the animal in the prone position with the head extended. The dura was opened and the temporal cortex stimulated using a monopolar electrode (plate 1).

Stimulus No.	*Voltage*	*Frequency*	*Pulse Duration*	*Response*
1.	8	10/sec.	5 msec.	e – Slight ipsilateral eyelid
2.	"	"	"	e – Slightly better ipsilateral eyelid
3.	9	"	"	F – Strong ipsilateral face
4.	"	"	"	e – Very slight ipsilateral eyelid
5.	"	"	"	Fn – Ipsilateral face and strong neck
6.	"	"	"	F – Ipsilateral face
7.	"	"	"	F – Marked ipsilateral face
8.	"	"	"	e – Slight ipsilateral eyelid
9.	"	"	"	e – Slight ipsilateral eyelid

There was an unequivocal specificity of response to all stimuli. After completion of stimulation, the area of the left temporal cortex from which the ipsilateral movements were obtained was excised to a depth of 5 to 6 mm. using suction primarily, and only employing the electrocautery for coagulation of one or two cortical vessels. This region is shown as a stippled area in plate I. The site of excision (figure 1) was then restimulated and no ipsilateral response obtained. Postoperatively the animal was less aggressive for the first two days and then returned to his normal behavior.

Protocol No. 2 – Monkey No. 1 (Macaca mulatta)

On May 11, 1951, three weeks after the first procedure, a right frontotemporal craniotomy was performed in the prone position with the head hyper-

PLATE 2. Drawing of the macaque brain showing the regions of the right hemisphere from which movements were elicited on stimulation in monkey No. 1. For interpretation of legends, see protocol No. 2.

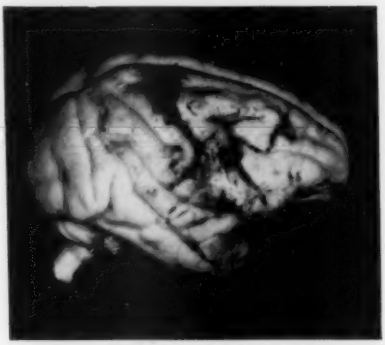


FIG. 2. Sites of cortical excision of right hemisphere, the tip of temporal lobe and part of Area 4. Discoloration due to fixation.

extended. The dura was opened and stimulation of the frontal cortex carried out using a monopolar electrode (plate 2).

Stimulus No.	*Voltage*	*Frequency*	*Pulse Duration*	*Response*
1.	8	10/sec.	5 msec.	d' – Contralateral horizontal conjugate deviation
2.	"	"	"	d' – Contralateral horizontal conjugate deviation

The motor strip (area 4) was now tested for contralateral movements of the face, body, and extremities. Because of the initiation of convulsive movements, the voltage had to be reduced to 7 volts. The following results were obtained from the motor and temporal cortices.

Stimulus No.	*Voltage*	*Frequency*	*Pulse Duration*	*Response*
3.	9	10/sec.	5 msec.	FF'n's' – Entire face with contralateral neck and shoulder
4.	8	"	"	FF'n's' – Same but less marked
5.	7	20/sec.	"	m – Ipsilateral mouth
6.	8	"	"	FF'a' – Entire face with contralateral arm
7.	7	30/sec.	"	F – Ipsilateral face. (After response of extension of both arms and flexion of contralateral fingers.)
8.	"	"	"	F' – Contralateral face
9.	"	"	"	mm' – Bilateral pursing of lips
10.	"	"	"	a' – Contralateral arm

The portion of area 4 from which contralateral face movements were evoked was excised (figure 2). Stimulation of the ipsilateral temporal cortex, following this procedure, gave the following responses.

Stimulus No.	*Voltage*	*Frequency*	*Pulse Duration*	*Response*
1.	7	40/sec.	5 msec.	F – Ipsilateral face
2.	"	"	"	F – Ipsilateral face
3.	"	"	"	F – Ipsilateral face

The tip of the right temporal lobe from which the ipsilateral facial responses had been obtained was then excised to a depth of 5 to 6 mm. (figure 2). After the excision, stimulation of the region no longer produced ipsilateral movement. Postoperatively the monkey appeared to be generally slowed down in his behavior, but no paresis or paralysis was evident.

Comment: Since the left temporal "second" or "additional" motor area for ipsilateral movements had previously been removed, it was interesting to note that stimulation of the right motor area (area 4) still produced contralateral or left facial movements. Also, excision of the right motor area (area 4) had no effect upon the ipsilateral movements derived from stimulation of the "second" motor area on the tip of the right temporal lobe. Finally, these ipsilateral movements were completely abolished by excision of the cortex at the tip of the right temporal lobe.

Protocol No. 3 – Monkey No. 2 (Macaca mulatta)

This animal had had a previous operative lesion which had destroyed the flocculus on the right side, but there was no obvious residual neurologic deficit. On May 25, 1951, a right frontotemporal craniotomy was performed in the supine position with the face directly upward. Stimulation of the motor cortex and the temporal lobe was carried out (plate 3). A monopolar electrode was used in this series.

Stimulus No.	*Voltage*	*Frequency*	*Pulse Duration*	*Response*
1.	9	10/sec.	5 msec.	n – Ipsilateral neck
2.	"	30/sec.	"	F – Ipsilateral face
3.	"	40/sec.	"	F' – Contralateral face
4.	"	"	"	h'f' – Contralateral hand and forearm
5.	"	30/sec.	"	Fn – Ipsilateral face and neck
6.	7	"	"	$\underline{F}$ – Ipsilateral face
7.	8	40/sec.	"	$\overline{F}$ – Ipsilateral face
8.	9	"	"	$\underline{F}$ – Ipsilateral face
9.	"	"	"	$\overline{Fn}$ – Ipsilateral face and neck
10.	"	"	"	Fn – Ipsilateral face and neck

In the regions where ipsilateral face movement ($\underline{F}$) is found, there was a tendency for extension of the lower extremities bilaterally as an after response, but this extension appeared to be more marked ipsilaterally. Restimulation was performed. The right motor and sensory areas functionally related to contralateral face movements were removed (figure 3) and the right temporal lobe again stimulated with the following results.

PLATE 3. Drawing of the macaque brain showing the regions of the right hemisphere from which movements were elicited on stimulation in monkey No. 2. For interpretation of legends, see protocol No. 3.

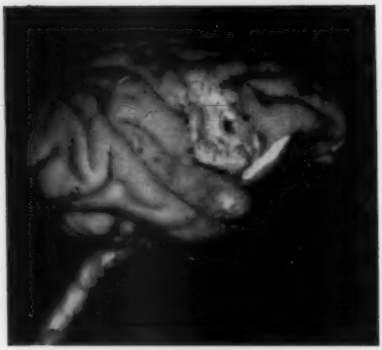


FIG. 3. Cortical excision site in right frontoparietal area. Contusion of tip of temporal lobe but no excision has been performed at that point.

Stimulus No.	*Voltage*	*Frequency*	*Pulse Duration*	*Response*
1.	10	40/sec.	5 msec.	Fnll' – Ipsilateral face, neck and extension of the lower extremities (more marked ipsilaterally) and tail
2.	"	"	"	sll' – Ipsilateral shoulder; extension of lower extremities (more marked ipsilaterally)
3	9	"	"	Fll' – Ipsilateral face; extension of lower extremities (more marked ipsilaterally)

On stimulation of the tip of the right temporal lobe an ipsilateral face response was elicited identical to that obtained in monkey No. 1; this response persisted even after excision of the motor (area 4) and sensory areas for contralateral face movements. Upon restimulation of the right temporal region, ipsilateral face movements were evoked with a tendency for extension of both lower extremities but with a more pronounced response ipsilaterally.

Protocol No. 4 –Monkey No. 2 (Macaca mulatta)

One week previously, this animal had had a right frontotemporal craniotomy with excision of the portions of the motor and sensory cortices related to contralateral face movements. On June 1, 1951, a left frontotemporal craniotomy was performed in the supine position with the face directly upward. The dura was opened and the temporal and motor cortices stimulated (plate 4). A monopolar electrode was used for stimulation.

The region of the left temporal lobe cortex from which the ipsilateral responses had been obtained was excised to a depth of 5 to 6 mm. using suction and an electrocautery for coagulating a few vessels (figure 4). Upon restimulation of the area there was no motor response.

The ipsilateral response to temporal lobe stimulation persisted in spite of the fact that the primary contralateral motor area (area 4) and the sensory

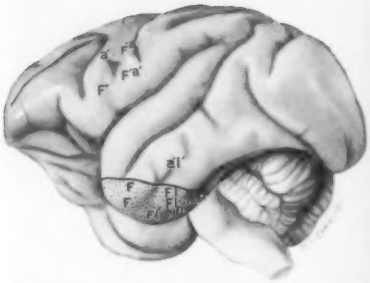


PLATE 4. Drawing of the macaque brain showing the regions of the left hemisphere from which movements were elicited on stimulation in monkey No. 2. For interpretation of legends, see protocol No. 4.

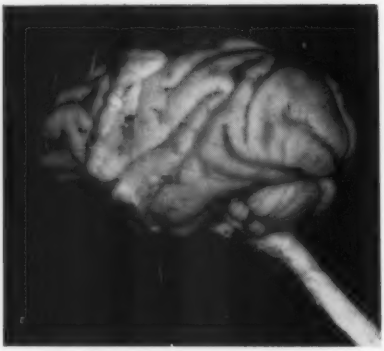


FIG. 4. Cortical excision of tip of left temporal lobe.

Stimulus No.	*Voltage*	*Frequency*	*Pulse Duration*	*Response*
1.	9	30/sec.	5 msec.	F′ – Contralateral face
2.	"	"	"	a′ – Contralateral arm
3.	"	"	"	F′a′ – Contralateral face and arm
4.	"	"	"	F′a′ – Contralateral face and arm
5.	"	"	"	Fl – Ipsilateral face and leg
6.	"	"	"	F – Ipsilateral face
7.	"	"	"	F – Ipsilateral face
8.	"	40/sec.	"	Fl – Ipsilateral face and leg
9.	"	"	"	m – Ipsilateral mouth
10.	"	"	"	Fl′ – Ipsilateral face and contralateral leg
11.	"	"	"	Fl – Ipsilateral face and leg
12.	"	"	"	m – Ipsilateral mouth
13.	"	"	"	Fl – Ipsilateral face and leg
14.	"	30/sec.	"	a′l′ – Contralateral arm and leg

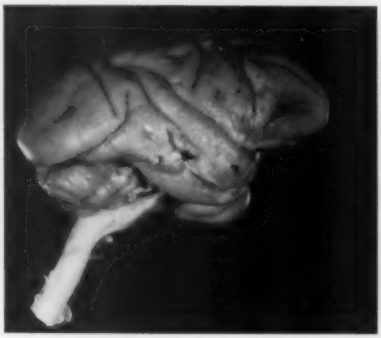
area had been excised a week previously. Therefore, the "second" motor area in the temporal lobe related to ipsilateral movements appears to be able to function independently of a discharge through the contralateral motor and sensory cortices. Also, in this animal a combined response of ipsilateral face and leg movements, as well as ipsilateral facial movements alone, were obtained on several occasions. This type of response was evoked in the inferior temporal gyrus posterior to the region where purely ipsilateral face movements had been elicited.

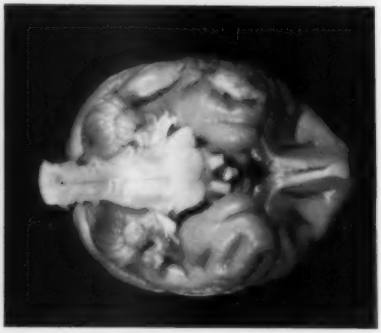
Protocol No. 5 – Monkey No. 3 (Macaca cynomolgus)

On June 29, 1951, a right frontotemporal craniotomy was performed in the supine position with the face directed upward. The dura was opened. Under conditions comparable to those in previous experiments (9 volts, 30/sec. frequency, and 5 msec. pulse duration) stimulation produced no response from

PLATE 5. (*left*) Drawing of the macaque brain showing the regions of the right hemisphere from which movements were elicited on stimulation in monkey No. 3. For interpretation of legends, see protocol No. 5.

FIGS. 5 and 6. (*below*) Excision of cortex of the anterior portion of the right temporal lobe.





either the motor cortex (area 4) or the cortex at the tip of the temporal lobe. However, after increasing the strength of the stimulus, accurate responses were produced from the temporal cortex (plate 5). A bipolar electrode was used for stimulation.

Stimulus No.	*Voltage*	*Frequency*	*Pulse Duration*	*Response*
1.	14	40/sec.	5 msec.	Fs' – Ipsilateral face – contralateral shoulder
2.	"	"	"	F – Ipsilateral face
3.	"	"	"	Fss' – Ipsilateral face and bilateral shoulders
4.	"	"	"	Fss' – Ipsilateral face and bilateral shoulders (more marked ipsilateral)
5.	"	"	"	Fs – Ipsilateral face and shoulder
6.	"	"	"	Fss' – Ipsilateral face and bilateral shoulders
7.	"	"	"	Fss' – Ipsilateral face and bilateral shoulders
8.	"	"	"	Fstt' – Ipsilateral face and shoulder and bilateral toes
9.	"	"	"	tt' – Bilateral toes

The entire tip of the right temporal lobe was then excised to a depth of 5 to 6 mm. (figures 5 and 6). On restimulating the ablated area and its periphery no motor response could be evoked.

Cynomolgus apparently has a higher threshold to stimulation than Macaca mulatta, for the stimulus required to produce similar responses was almost twice as great for the former animal. However, when these responses were elicited they were directly comparable with those obtained in Macaca mulatta and they were again abolished by ablation of the tip of the right temporal lobe.

PLATE 6. Drawing of the macaque brain showing the regions of the left hemisphere from which movements were elicited on stimulation in monkey No. 4. For interpretation of legends, see protocol No. 6.

FIG. 7. Sites of cortical excision bifrontally.

Protocol No. 6 – Monkey No. 4 (Macaca mulatta)

A left frontotemporal craniotomy was performed on December 28, 1951. Varying parameters of stimulation were used until responses were obtained from the temporal pole and from the motor cortex (plate 6). A bipolar electrode was used for stimulation.

Stimulus No.	*Voltage*	*Frequency*	*Pulse Duration*	*Response*
1.	9	50/sec.	5 msec.	F' – Contralateral face
2.	5	"	"	F' – Contralateral face
3.	6	"	"	F' – Contralateral face
4.	7	"	"	F – Ipsilateral face
5.	7	"	"	F – Ipsilateral face
6.	6	"	"	F – Ipsilateral face
7.	6	"	"	F – Ipsilateral face
8.	5	"	"	F – Ipsilateral face

Areas 4 and 6 (stippled) were removed to a depth of 5 to 6 mm. (figure 7). Restimulation of the region underlying the ablated area no longer produced contralateral facial movements. Postoperatively there was a minimal paresis of the right upper extremity but the lower extremity had almost normal movements. Facial movements could not be well evaluated.

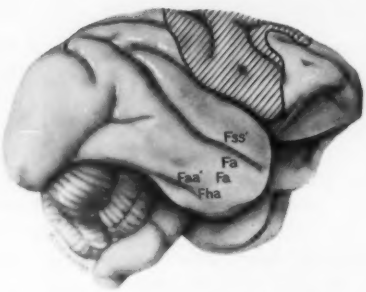


PLATE 7. Drawing of the macaque brain showing the regions of the right hemisphere from which movements were elicited on stimulation in monkey No. 4. For interpretation of legends, see protocol No. 7.

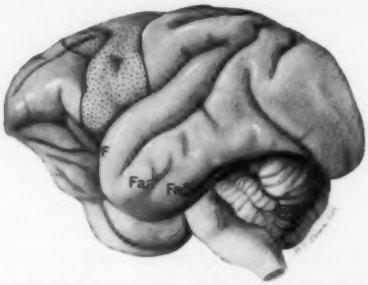


PLATE 8. Drawing of the macaque brain showing the regions of the temporal cortex restimulated after reopening the left frontotemporal craniotomy wound in monkey No. 4. For interpretation of legends, see the final list of responses presented in protocol No. 7.

Protocol No. 7 – Monkey No. 4 (Macaca mulatta)

This animal had had a left frontotemporal craniotomy one week previously, with excision of areas 4 and 6 on the left (plate 6). The left temporal region was intact. A right frontotemporal craniotomy was performed and the right temporal cortex stimulated (plate 7). A bipolar electrode was employed for stimulating throughout the following series.

Stimulus No.	*Voltage*	*Frequency*	*Pulse Duration*	*Response*
1.	11	70/sec.	5 msec.	Fa – Ipsilateral face and arm
2.	9	"	"	Fa – Ipsilateral face and arm

The right motor and sensory areas were totally removed (figure 7). Stimulation of the right temporal lobe then gave the following responses:

Stimulus No.	*Voltage*	*Frequency*	*Pulse Duration*	*Response*
3.	9	70/sec.	5 msec.	Fss' – Ipsilateral face and shoulder bilaterally
4.	8	"	"	Fha – Ipsilateral face and hand, ipsilateral arm
5.	7	"	"	Faa' – Ipsilateral face with bilateral extension of arms

The previous left frontotemporal craniotomy wound was reopened and the left temporal cortex restimulated (plate 8).

Stimulus No.	*Voltage*	*Frequency*	*Pulse Duration*	*Response*
1.	8	70/sec.	5 msec.	F – Ipsilateral face
2.	"	"	"	Faa' – Ipsilateral face and bilateral extension of arm
3.	"	"	"	Faa' – Ipsilateral face and bilateral extension of arm

SUMMARY

There is a "second" or "additional" motor area in the temporal lobe of the monkey which, upon stimulation, will evoke ipsilateral facial movements. This area is located at the tip of the temporal lobe, in the superior and middle temporal gyri, and particularly in the lateral and basal portions of the inferior temporal gyrus.

These face movements are combined frequently with shoulder and arm movements when the middle and inferior temporal gyri are stimulated and particularly with leg movements when the inferior temporal gyrus is the site of stimulation. Farther back in the temporal lobe there is some indication that arm and leg movements may be obtained independently of motor responses of the face.

The assistance of Dr. Edward W. Lauer and Dr. Robert E. Yoss of the department of anatomy in carrying out the operative procedures for this report is acknowledged with sincere thanks. The authors also wish to express their appreciation for the figures drawn by Miss Mary L. Cummings, medical illustrator, University Hospital, Ann Arbor.

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Effects of Intrathecal Mephenesin in Paraplegia

Louis Berlin, M.D.

MANAGEMENT OF THE PARAPLEGIC PATIENT is complicated by such difficulties as violent and often painful involuntary movements and the development of flexion contractures. Mephenesin has been reported to be capable of reducing the rigidity of the extremities produced by spinal cord lesions and at the same time increasing motor power.[1] However, oral administration has proved ineffective in altering the involuntary movements, contractures, or motility functions of paraplegic patients. Intravenous injection of mephenesin has some relaxing effect on the spastic extremities, but this effect is short-lived, and doses adequate to effect relaxation often result in generalized weakness and somnolence. It was decided to investigate the effect of injection of 2 per cent mephenesin into the lumbar cistern and to ascertain whether this would safely achieve prolonged relaxation of paraplegic limbs.

SUBJECTS AND METHODS

The subjects were six adult men, all of whom had severe spastic paraplegia with spontaneous involuntary flexor movements of the lower extremities. All patients could move their upper extremities voluntarily and had adequate ventilatory capacities. Three patients had multiple sclerosis, one had a metastatic carcinoma at T2-4, one had erosion of the vertebrae of T5-8 by an aneurysm, and the sixth patient had a mild spastic paraparesis following an anterolateral cordotomy at C7. Vital capacity and the voluntary movement of the upper and lower extremities were ascertained for each patient before and after intrathecal injection. Bipolar needle electrodes were inserted into the calf and thigh and connected to a Grass electroencephalograph. The potentials set up in these muscles by a single stroke on the sole of the foot with a blunt wooden applicator were recorded. A total of 10 to 20 cc. of a 2 per cent aqueous solution of mephenesin was injected in the lumbar cistern over a 15 to 30 minute period.

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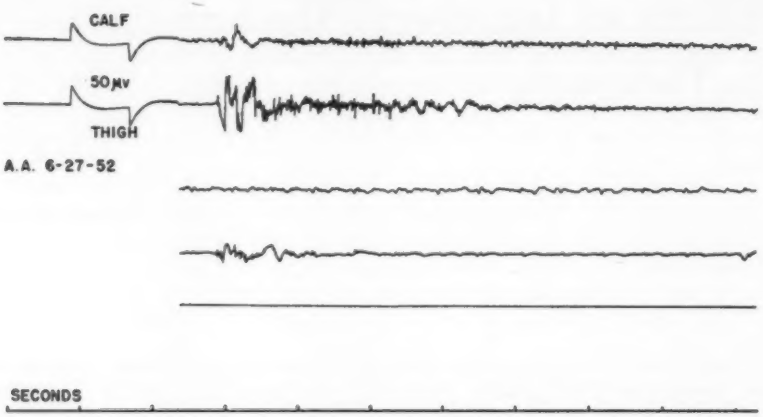


FIG. 1. The first two tracings are electromyographic responses of the gastrocnemius and rectus femoris to plantar stimulation. The third and fourth tracings are responses similarly elicited one minute after the injection of 3 cc. of 2 per cent mephenesin into the lumbar cistern.

EFFECT ON REFLEX MOTOR FUNCTIONS

Prior to mephenesin injection marked flexor movements were readily elicited by a single stroke on the sole of the foot with a wooden applicator (figures 1 and 2A). Within one minute after the injection of as little as 3 cc. of 2 per cent mephenesin into the lumbar cistern there was a striking reduction in the withdrawal response to plantar stimulation (figure 1). In one instance the injection of 4 cc. of 2 per cent mephenesin over a five minute period was followed by complete abolition of motor responses to plantar stimulation. Injection of 10 to 15 cc. over a 15 to 30 minute period completely abolished spontaneous and induced flexor withdrawal movements, ankle clonus, deep tendon reflexes, and extensor plantar responses in all patients. The flexor movements, deep tendon reflexes, clonus, and extensor plantar responses returned in 90 to 120 minutes after completion of the first injection of 15 cc. However, it was apparent that although return of these reflex motor functions had occurred in that time, the motor responses were not as active as they had been prior to the injection. Reflex motor activity was reduced for at least three to five days after the injection. Repeated injections of 15 cc. given at three to seven day intervals had the effect of gradually reducing the range and frequency of spontaneous flexor movements, deep tendon reflexes, and the responses to plantar stimulation (figure 2). The reduction of motor activity was most pronounced in the distal parts of the extremities, as evidenced by the loss of ankle clonus and the extensor plantar response. Involuntary movements of the thighs persisted but were reduced in range and frequency. After 11 injections averaging 15 cc. each over a 12 week period given to one patient and 10 injections over a 20 week period given to another, ankle clonus

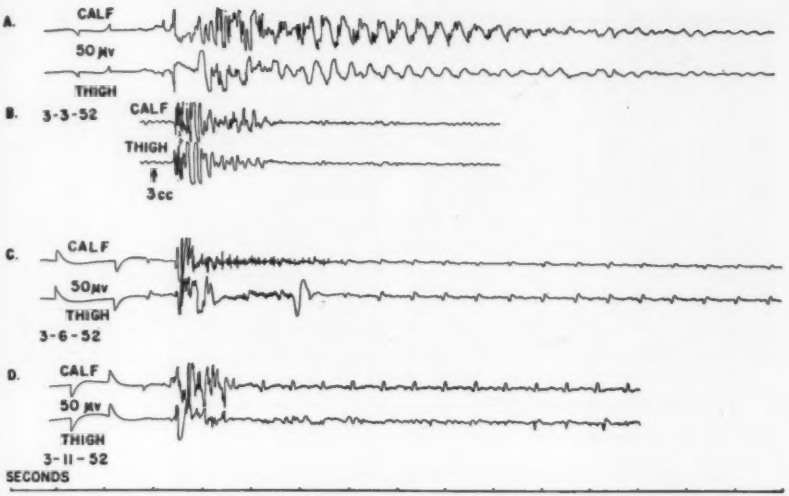


FIG. 2. A, C, and D, are electromyographic responses of thigh and calf muscles to plantar stimulation prior to injection of mephenesin on the respective days. B demonstrates the reduced reaction to plantar stimulation after injection of 3 cc. of 2 per cent mephenesin. Fifteen cc. of 2 per cent mephenesin were injected on each of these days after recordings of responses to plantar stimulation. There is a progressive decline in responsiveness three and five days (C and D), respectively, after the preceding injections. Electrocardiographic artefacts are present in C and D.

and extensor plantar responses were abolished, but slight flexor movements of the thighs still occurred in response to noxious stimuli. In a third patient, a total of 50 cc. of 2 per cent mephenesin given in three injections over a six day period caused the abolition of deep tendon reflexes, ankle clonus, and the extensor plantar response, and reduction of the patellar reflexes. This change in the neurologic status persisted until the patient's death from carcinoma three weeks after the last injection.

EFFECT ON VOLUNTARY MOTOR PERFORMANCE

Three subjects had some voluntary movement in their lower extremities, such as the ability to move the toes or flex the feet, and one patient was able to walk. As the resistance to passive stretch and involuntary flexor movements were reduced during the injection, the subject's ability to move the extremities voluntarily was also reduced. Similarly when the spontaneous flexor movements failed to return to their preinjection level after repeated injections, the voluntary muscle strength was also permanently reduced. Hence there was no selective depressive effect on the resistance to passive stretch, flexor movements, or voluntary movement, but all were reduced during the injection. Furthermore, there was a residual depression of these functions that persisted for many days after the injection.

Strength of the upper extremities was unaffected by the injection in the lumbar cistern.

EFFECTS ON RESPIRATORY, BLADDER, AND VASOMOTOR FUNCTIONS

Vital capacity measurements were made prior to and immediately after each injection, but were not affected by the amount of drug injected. On one occasion, 30 cc. of 2 per cent mephenesin was injected over a one hour period without affecting respiratory function or strength of the upper extremities.

Two of the paraplegic subjects were able to urinate spontaneously. After a single 10 cc. injection they were unable to empty their bladders, and they required catheterization for four and seven days, respectively, before they were able to void spontaneously.

There were no significant changes in skin temperature of the extremities after the injections. Blood pressure also was unaffected.

Electroencephalographic records taken on all patients before and during the injection were unchanged.

EFFECTS ON SENSATION

Three patients had some remaining sensory function in the lower extremities, but during the injection they reported that their legs felt "dead" or "numb." Two patients were tested by the Hardy-Wolff-Goodell method for ascertaining pain threshold.[2] In one patient pain threshold of the right leg was 290 millicalories/sec/cm^{-2}. Fifteen minutes after the 10 cc. injection the pain threshold rose to over 400 millicalories/sec/cm^{-2}. Furthermore, the patient did not perceive the heat that precedes pain when this method of pain testing is employed. The pain threshold in the left foot of another patient was 300 millicalories/sec/cm^{-2} before injection and rose to over 400 millicalories/sec/cm^{-2} after the injection. The elevation of pain threshold in the legs following repeated injections was sustained, and this was reflected in the reduction of pin prick perception for many months.

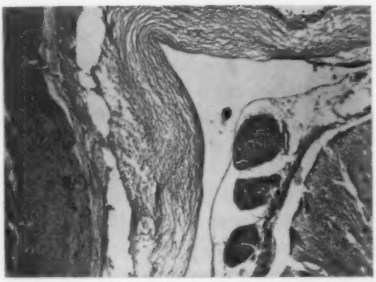
The acuity of position and vibration senses was reduced immediately after the injections.

There was no pain produced during or after the injections into the lumbar cistern.

EFFECTS ON SPINAL FLUID

The specific gravity of 2 per cent mephenesin was 1.009 and its pH 6.9. The solution was readily miscible with the spinal fluid.

The spinal fluid of one patient contained one mononuclear cell and 28 mg. per 100 cc. of protein prior to injection. During the next three months he received 11 injections, and the fluid became xanthochromic, the protein increased to 3.3 gm., but there was no increase in cells. These changes were in part due to a complete spinal block by a metastatic tumor. In another patient without tumor or block, there was a gradual elevation of the spinal fluid protein from 41 mg. per 100 cc. to a maximum of 112 mg. per 100 cc., and a gradual reduction to 49 mg. per 100 cc. during a ten month period.



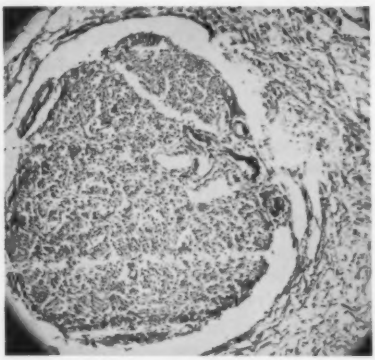


FIG. 3. Thickening of the arachnoid and arachnoidal-dural adhesions in the lumbar region following repeated injections of 2 per cent aqueous solution of mephenesin. Azocarmine stain.
FIG. 4. Preservation of the axones of a lumbar root despite thickening of the arachnoid. Bodian stain.

The maximum cellular response was 11 lymphocytes. In a third patient the spinal fluid protein rose from an initial value of 37 to 59 mg. per 100 cc. five days after an injection, but there was no increase in cells.

EFFECTS ON TISSUES

One patient who had had 11 injections died of bronchogenic carcinoma. The epidural and subdural spaces in the lumbar and lower thoracic regions were incompletely obliterated by adhesions. Histologic examination revealed a fibrous thickening of the arachnoid with little inflammatory cellular infiltration (figure 3). Nissl and hematoxylin and eosin stains showed that the gray matter of the cord was intact. No areas of demyelinization of the cord were evident in the Weil stained sections. Bodian silver stains for axones failed to show any degeneration (figure 4). The dorsal root ganglia were intact.

Another patient who received five injections died from a systemic illness attendant upon multiple sclerosis. He showed similar but milder changes, that is, a fibrous thickening of the arachnoid.

One patient with multiple sclerosis had residual contractures at the hips and knees after 11 injections, for which a rhizotomy was performed two months after the last injection. A biopsy of the arachnoid showed fibrous proliferations and mild lymphocytic infiltration.

DISCUSSION

Previous observations have indicated that mephenesin administered orally or intravenously acts rapidly on the brain stem and spinal cord to overcome increased resistance to passive stretch, involuntary movements, and hyperflexia.[1,3] There is also evidence that, although capable of inducing paralysis,

the agent in doses of 30 to 80 mg./kilo does not affect the myoneural junction or peripheral nerve function.[4] If it can be said with certainty that mephenesin has no action on peripheral nerve function, then it can be deduced that the intrathecal injection of mephenesin is capable of affecting the spinal cord to alter the motility functions of patients with spinal cord lesions. As little as 40 mg. mephenesin given intrathecally to an adult male can abolish deep tendon reflexes and flexor responses to cutaneous stimuli. To achieve a similar effect in an adult man by intravenous administration of the drug, a dose 40 to 60 times this amount is needed. Oral doses of 2 gm. often fail to produce similar changes in motor responses.

It has been observed repeatedly that the action of mephenesin is brief and readily reversible. Following intrathecal injection, however, the decrease in motor responsiveness is protracted over many days and the effect may be permanent. Whether the prolonged effect is attributable to the development of an arachnoiditis, a specific toxic effect, or the pharmacologic action of the drug is not clear. The decrease of motor hyperactivity of the extremities for several days after even the first injection tends to exclude a cicatricial arachnoiditis as the sole responsible factor, since it seems unlikely that this reaction would develop so rapidly.

Although the agent is used for its action on the motor mechanisms of the brain stem and spinal cord, it is obvious that it affects other neural functions. It diminishes pressor responses resulting from stimuli to the bulbar reticular formation.[5] Reduction of the ability to urinate produced in our patients points to another effect on autonomic function.

Mephenesin is capable of altering sensory function. It has been found to relieve thalamic pain[6] and the pain of causalgia.[7] Libet[8] has observed that there is an anesthetic effect and there is a "semipermanent retention of the local anesthetic action when the drug is injected around superficial nerves." A local anesthetic action has been observed when the drug is applied to the cornea.[3b]

Thus far the only tissue damage noted has been thrombophlebitis at the site of injection.[9] Repeated intrathecal injection is capable of inducing an arachnoiditis and hence should be used repeatedly only when the patient's general status makes the development of arachnoiditis a minor consequence. In cases of irreversible paraplegia, intrathecal injection may prove useful in overcoming contractures and painful flexor movements.

SUMMARY AND CONCLUSIONS

1. The injection of as little as 3 cc. of 2 per cent mephenesin into the lumbar cistern of six paraplegic adult males caused a marked reduction of spontaneous and induced flexor movements and abolition of clonus and deep tendon reflexes.

2. With the reduction of simple reflex motor activity of the lower extremities, there was a simultaneous reduction of voluntary motor functions of the lower extremities.

3. The reflex motor phenomena and voluntary motility returned maximally in 90 to 120 minutes after the injection of 10 to 15 cc. of 2 per cent mephenesin, but there was a residual depression of both these functions for many days after the injection. This depressant effect was also observed in the ability to empty the urinary bladder.

4. The injection of mephenesin into the lumbar cistern caused a marked elevation of the pain threshold, an effect which was sustained for several days following the injection.

5. In three patients there was histologic evidence of an adhesive arachnoiditis after repeated injections.

6. The injection of mephenesin into the lumbar cistern caused a rapid reduction in the sensory and the voluntary and reflex motor functions of patients with severe spinal cord lesions.

7. Intrathecal injection of 2 per cent mephenesin may be useful for the relief of contractures and painful involuntary flexor movements resulting from lesions causing severe irreversible paraplegia.

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A practical remark by Dr. Reynolds on the treatment of epilepsy is equally applicable to the case of megrim: "Too great importance," he thinks, "cannot be attached to *regularity* of hours, not only in regard of the fact of taking food, but in respect of both its quantity and quality. A similar kind of meal should be taken at the same hours daily, and with great punctuality."

Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

Afferent Projection of the Superior Laryngeal Nerve in the Brainstem

Robert L. Lam, M.D. and Joseph H. Ogura, M.D.

PREVIOUS ELECTROPHYSIOLOGIC STUDIES have demonstrated a remarkably discrete projection system of the superior laryngeal nerve in the cerebellum of the cat.[1] During the course of these experiments, the medulla was likewise explored and a precise region of representation found in the dorsal reticular formation at the level of the hypoglossal nucleus.

METHOD

Ten cats of fairly uniform size (2.0 to 2.5 kg.) were given intraperitoneal Nembutal in a dosage of 30 mg. per kg. body weight. Endotracheal ether was subsequently used through a tracheotomy to maintain a stable preparation with a moderate depth of anesthesia. The cervical vagus, nodose ganglion, and superior laryngeal nerve were exposed by careful dissection. Each animal was then immobilized in a specially devised rack, rotated 75 degrees along the longitudinal axis. The brainstem and cerebellum and the ventral cervical structures were then easily accessible to dissection and manipulation.

The superior laryngeal nerve was freed from the nodose ganglion to the thyrohyoid membrane, and the motor branch identified and separated. Only the major sensory nerve was used for stimulation. After section at the thyrohyoid membrane, the nerve was placed on No. 24 nichrome wire electrodes, insulated with plastic except for the stimulating surfaces beneath the nerve. Care was taken to avoid any contact with other tissues. Dessication was prevented by mineral oil.

Exploration of the brainstem and cerebellum was carried out by 100 μ tip silver electrodes manipulated in all principal planes by an adapted microscope stage mounted on the head holder. The critical electrode was led against a periosteal reference in the vertex of the skull.

Single shocks were delivered to the superior laryngeal nerve through an isolation transformer and evoked potentials were recorded from the medulla on the cathode ray oscilloscope. Threshold stimuli will be considered by the unit 1, and supraliminal stimuli as its multiples.

From the departments of neuropsychiatry and otolaryngology, Washington University School of Medicine, St. Louis, Missouri.

Read at the sixth annual meeting of the American Academy of Neurology, Washington, D.C., April 30, 1954.

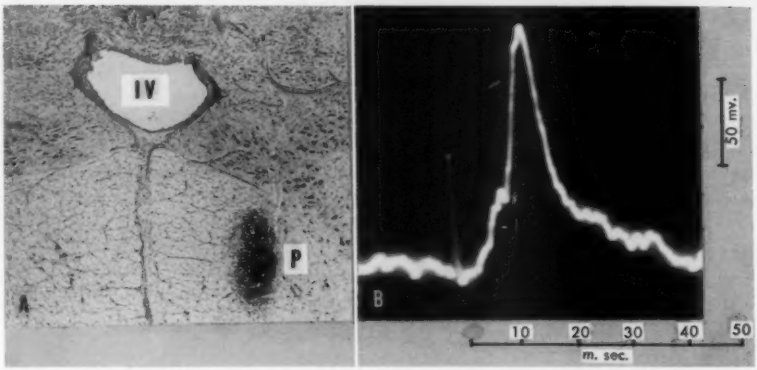

FIG. 1. A. Section of cat medulla at level of hypoglossal nucleus and calamus scriptorius. *P*, point of electrolysis indicating locus of maximum response on stimulating superior laryngeal nerve. B. Typical monophasic response recorded from area indicated at *P* on stimulating the superior laryngeal nerve.

In the cat, the calamus scriptorius can be easily identified and the posterior portion of the fourth ventricle region explored without disturbing the cerebellum. In six experiments both cerebellar and medullary response areas were studied, the cerebellum always being investigated first.

RESULTS

At relatively low stimulus strengths, activation of the "A" fiber component of the superior laryngeal nerve evoked a positive monophasic 100 to 250 microvolt response in the ipsilateral dorsal reticular formation beneath the hypoglossal nucleus and medial to its ventrad directed fibers (figure 1). Occasionally, a diphasic response could be elicited with an initial very small negative phase. Latent period varied from 8 to 12 msec. from experiment to experiment. No additional responses could be produced at higher stimulus strengths sufficient to activate the "B" fibers of the nerve. No responses were recorded from the dorsal vagal sensory nucleus or from the nucleus solitarius.

After each experiment the length of the superior laryngeal nerve from the point of stimulation to the response locus in the brainstem was calculated; it usually ranged from 40 to 50 mm.

DISCUSSION

The large evoked response in the reticular formation of the medulla at the level of the calamus scriptorius represents a post-synaptic potential. In calculating the expected latent period for such a response there is a considerable discrepancy of about 6 to 8 msec. The velocity of the "A" potential being 25 to 30 M/sec.[1] in the superior laryngeal nerve of the cat and the total distance being about 40-50 mm., one would expect a latent period of about 3 msec. for the medullary response at the first synapse. The long latent period

of 8 to 12 msec. suggests a multisynaptic pool that gradually produces a rising potential of large amplitude.

The finding of a locus of potentia maxima in the dorsal reticular formation of the medulla on stimulating the superior laryngeal nerve indicates the tremendous importance that the reticular nuclei play as a discharge center mediating reflex functions at the brainstem and spinal cord levels. Sjoblom[2] has reported apnea on afferent stimulation of the superior laryngeal nerve. Anderson, Landgren, Neil, and Zotterman[3] noted, in addition to apnea, reflex augmentation of intestinal mobility on stimulating the proximal end of the cat's superior laryngeal nerve. Johnson[4] showed reflex mucous secretions on stimulation of the central end of the superior laryngeal nerve. On stimulation of the human superior laryngeal nerve, we have observed sudden reflex closure of the vocal cords.[5]

The presence of cerebellar projection areas in Crus I and paramedianus suggests that the reticular center of the superior laryngeal nerve may represent a significant way station for complex coordinating functions subserved by the cerebellum.

CONCLUSIONS

1. Stimulation of the proximal end of the cat superior laryngeal nerve evokes potentia maxima in the dorsal reticular formation of the medulla.

2. The reflex functions of the reticular formation in relation to afferent laryngeal stimuli are strongly inferred.

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CASE REPORT

Chronic Epidural Abscess and Condensing Osteomyelitis of the Skull

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THIS REPORT is one of a case of chronic epidural abscess characterized clinically by peculiar findings and association with chronic osteomyelitic changes rarely seen in the skull. Epidural abscesses are most commonly caused by infections of the mastoid[1] or frontal sinuses and at times by osteomyelitic processes of the vault.[2] They very rarely reach the chronic stage because, if not treated surgically, the outcome is usually fatal. The size of the cavity is ordinarily small or, in any case, too small to produce clinical evidence of impaired cerebral function.[3] Calcification of the abscess wall occurs occasionally.

CASE REPORT

A 51 year old white, right handed man had suffered from a nontraumatic osteomyelitis of the right tibia at the age of four. This cleared up in about six years. At age 25 the patient complained of slight headaches, and some time later the scalp over the right frontoparietal area appeared swollen. A fistula developed which discharged pus intermittently. No rise in temperature was recorded and the patient had no other complaints. He continued working until, at the age of 49, he became very slow in his psychomotor activity and noted dragging of his right leg. A year later the patient suddenly became completely paralyzed on the right side. The hemiplegia was accompanied by severe headaches, but was not associated with loss of consciousness or speech defect. At that time the temperature was elevated and there was considerable drainage of pus from the persisting sinus in the scalp. For the first time the patient received medical care; antibiotics were administered and the temperature slowly returned to normal. The patient appeared disoriented and irrational mentally, and he was admitted to Central Islip State Hospital on August 21, 1951. Here it was noted that when the patient sneezed or coughed spurts of pus occasionally appeared from the sinus. This had happened several times in the previous six years. When the purulent drainage diminished or stopped completely, it was also observed that the temperature rose, the level of consciousness became lower, the blood pressure dropped, the pulse was weak and rapid, the hemiplegia became worse, and the pupils appeared small and fixed. Antibiotics were administered each time a temperature elevation occurred.

Physical examination. On September 5, 1952, the patient was referred to the neurosurgical service. At that time examination revealed the following positive findings: 1)

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an old depressed scar in the medial aspect of the right leg; 2) asymmetry of the head, the right hemicircumference as measured from the glabella to the external occipital protuberance being 1 cm. larger than the left; 3) sinus tract over the right frontoparietal area about 4 cm. from the midline; 4) right hemiplegia with hyperactive deep reflexes, absent cutaneous reflexes, Babinski sign, and knee and ankle clonus. Mental examination showed markedly underproductive stream of mental activity, labile emotional reactions, no spontaneity, fair orientation, grossly impaired recent memory, impaired judgment, and lack of insight.

Laboratory data. Laboratory findings, including cerebrospinal fluid examination, were negative. Culture of the pus was positive for a nonhemolytic staphylococcus aureus sensitive to Aureomycin, Terramycin, and Bacitracin.

Roentgenographic examination. Roentgenograms of the skull showed the following: 1) considerable thickening of the entire right half of the skull, and, on the same side, marked elevation of the lesser wing of the sphenoid bone together with uniform enlargement of the orbital fissure; 2) a round, well defined defect in proximity to the coronal suture; 3) definite shift of the pineal gland to the left (12 mm.) and downward; 4) calcification of the falx (figure 1); and 5) a calcified line in the skull as shown in figure 2.

Angiogram of the right carotid artery showed simultaneous filling of the arterial and venous vessels. In the lateral views the pericallosal and the callosomarginal arteries appeared depressed. The superior longitudinal sinus was seen separated from the inner table of the skull in the region of the coronal suture. The anteroposterior view revealed marked shift of the anterior cerebral artery, downward displacement of the superior longitudinal sinus, and the existence of an avascular area underneath the bone delimited medially by cortical venous channels (figure 3).

Pneumoencephalography showed no filling of the ventricles. Air collected in the cortical subarachnoid space demonstrated separation of the brain surface from the inner table of the skull in the right frontoparietal area.

Electroencephalographic studies revealed a highly abnormal tracing with slow activity appearing from all areas of the cortex and an accentuation of the abnormality in the entire right hemisphere. Alpha activity was practically non-existent; delta activity was most prominent in the 5-6 c/s range.

The clinical and the radiologic findings seemed to substantiate the diagnosis of chronic osteomyelitis of the skull associated with epidural abscess.

First operation. Under general anesthesia a 7x6 cm. semicircular skin flap was turned in the right frontoparietal area, the middle of the incision corresponding to the sinus tract. Cicatricial tissue was noted around the sinus and this was excised together with the skin. The sinus tract in the bone was enlarged to the size of a burr-hole. The bone was so thick and hard that the rongeurs could not be used. To perform the craniectomy it was necessary to make three additional burr-holes, each one close to the other, and to break through the bone between them with a chisel. In this way a skull defect 5x5 cm. large was obtained. Dense yellowish pus welled up through a hole in a thick membrane attached to the inner table of the skull. After removal of a circular piece of the membrane a cavity filled with pus was seen. The cavity measured 8x9 cm. and was 2½ cm. deep, with a capacity of 70 cc. Necrotic membranes lined the walls of the abscess, and the dura forming the floor of the cavity was heavily calcified. A rubber drainage tube was led out from the cavity through an unclosed segment of the scalp incision.

Course. The patient was allowed out of bed 24 hours after operation and immediate improvement in his general status and in the hemiplegia was observed. Daily irrigations of the cavity with normal saline solution and antibiotics were done. Pink granulations slowly covered the dural calcifications and in about eight months the capacity of the cavity was 20 cc. Repeated cultures were negative. Hyperactive deep reflexes and slight dragging of the right leg were the only residuals of the hemiplegia and the patient was completely clear mentally. Routine postoperative electroencephalograms demonstrated progressive improvement, and eight weeks postoperatively the abnormality found was already minimal, being confined to the temporoparietal region. With a repeat pneumoencephalogram, filling of the ventricles and subarachnoid space was obtained. The ventricles appeared shifted to the left and downward. They were also asymmetric and deformed. The subarachnoid sulci on the left were better visualized and somewhat larger than normally seen. The right sylvian cistern appeared ele-

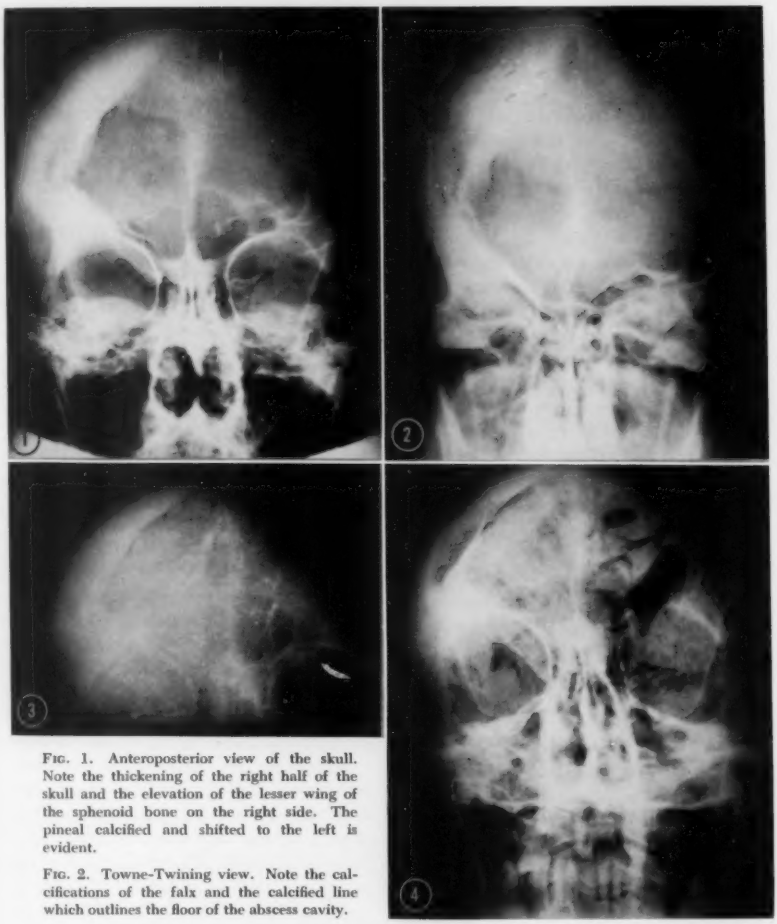

FIG. 1. Anteroposterior view of the skull. Note the thickening of the right half of the skull and the elevation of the lesser wing of the sphenoid bone on the right side. The pineal calcified and shifted to the left is evident.

FIG. 2. Towne-Twining view. Note the calcifications of the falx and the calcified line which outlines the floor of the abscess cavity.

FIG. 3. Angiogram of the right carotid artery. Arterial phase, showing the shift to the left of the anterior cerebral artery and the simultaneous filling of arterial and venous vessels. The superior longitudinal sinus appears markedly separated from the inner table of the skull.

FIG. 4. Postoperative pneumoencephalogram. Anteroposterior view, showing marked shift and deformation of the ventricular system. Note the elevation of the sylvian cistern on the right side.

vated as compared with the left (figure 4).

Because of the rigidity of the cavity, further surgical intervention was indicated.

Second operation. On July 27, 1953 under general anesthesia the cavity was completely exposed by removing the remaining thick bone forming the roof of the abscess. The fibrin layer containing the calcifications was scraped from the basic dural membrane and the scalp was collapsed on the dura. It was planned to repair the defect at a later time for a better cosmetic result.

COMMENT

It is not common to find marked neurologic findings in cases of chronic epidural abscess, because the cavity is usually small and because the dura acts as protection to the brain. A complete hemiplegia developed in this case because the abscess reached huge proportions. In fact, the abscess acted similarly to other space occupying lesions and produced marked shift of the cerebral hemispheres and of the brain stem. Presumably the hemiplegia, ipsilateral to the abscess, was produced by the known mechanism of encroachment of the cerebral peduncle on the tentorium. In this regard, it is interesting to note that the paralysis appeared long after the collection of pus had taken place. The operative and roentgenographic findings give good evidence that the abscess had been present for a long time and suggest that the thick and calcified dura acted as a barrier against the diffusion of the infection and minimized the pressure exerted on the brain. It is conceivable that, if the agent had been highly virulent and the formation of pus had occurred rapidly, the hemiplegia would have appeared earlier, probably with a fatal outcome. The dura very likely underwent the changes described before the abscess formed, that is, a pachymeningitis externa preceded the abscess. The drainage of pus from the sinus, acting as a safety valve, lowered the pressure on the brain and contributed to the chronic process of the abscess. It is significant that when the discharge of pus stopped, or when the amount of purulent exudate increased markedly, the level of consciousness dropped and the signs of paralysis became more pronounced. In view of the ipsilateral signs, this suggests brain stem involvement due to pressure and/or circulatory changes.

In the differential diagnosis between brain abscess and epidural or subdural abscess, the episodes of squirts of pus from the fistula seemed to offer clear evidence of an epidural collection.

In interpreting the findings revealed by radiologic examination, all the diseases which are known to produce thickening and condensation of the bones of the skull[4] were considered. We finally concluded that this was a case of condensing chronic osteomyelitis resembling the type which occurs in the long bones. Elevation of the lesser wing of the sphenoid bone and enlargement of the orbital fissure have been described previously in cases of slow growing, space-occupying lesions situated in the middle fossa or associated with other signs in cases of cerebral hemiatrophy. In the present case the abscess had a frontoparietal location, and there was no evidence of atrophy in the pneumoencephalogram. The marked shift of the cerebral hemisphere may have produced a wide separation of brain mass from the skull, particularly in the basal portion.

Regarding the arteriogram the most significant finding was the observation that the superior longitudinal sinus was depressed and separated from the inner table of the skull. The importance of this in differentiating a subdural from an epidural mass is obvious. As far as we know, the displacement of the superior longitudinal sinus as a sign of the presence of an epidural space occupying lesion has not been previously reported.

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CASE REPORT

An Unusual Case of "Diffuse Sclerosis" Occurring in Pregnancy

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ANY ACUTE NEUROLOGIC CRISIS occurring in a pregnant patient raises the question whether the pregnancy and the neurologic disease are related. Often pregnancy serves as a misleading factor in arriving at a definitive diagnosis because it is not related to the neurologic disease.

The following case is that of a patient who suffered an acute fatal neurologic disease in the sixth month of pregnancy. The unusual clinical course, the pathology, and the question of its relationship to pregnancy make it worthy of reporting.

SUMMARY

Sudden onset of headache, dizziness, fever, confusion, and right hemiparesis in a 25 year old primipara; grossly cloudy, sterile spinal fluid clearing in a few days after chemotherapy; positive blood culture for hemolytic *Staphylococcus aureus;* supervention of coma and decerebrate rigidity, and respiratory difficulty necessitating tracheotomy; terminal thrombocytopenic purpura; total duration of illness, 16 days. Necropsy: Extensive subcortical demyelination and softening, with considerable inflammatory reaction.

CASE HISTORY

A 25 year old white primipara in her sixth month of pregnancy had been examined by her obstetrician on August 31, 1951, and found to be perfectly well. The next day she experienced sudden onset of headache, spots before the eyes, dizziness, and mental confusion. When seen at home by her physician on the same day she appeared disoriented, had a temperature of 101° F., and was hospitalized immediately. Admission examination revealed a well developed and nourished woman with a staring expression, who was irrational and confused but presented no definite localizing neurologic signs and had only questionable neck rigidity. The pulse rate was 114, oral temperature 100.8° F., respirations 18 per minute, and blood pressure 126/68. Involuntary micturition occurred. The uterus was enlarged to the navel and fetal heart tones were audible.

The next day (September 2) a right hemiparesis was found. There was little power in the hand and foot. The Babinski sign was obtained from the right foot. The right abdominal reflexes were absent, but the left were brisk. A right lower facial weakness was present; the tongue deviated slightly to the right on protrusion. The Hoffmann sign, elicitable bilaterally, was more pronounced on the right side. Deep pain and pin prick sensation were perceived well. There was no significant neck rigidity and no Brudzinski sign. The pupils, external ocular movements, and fundi appeared normal; particularly, there was no nystagmus. Spinal puncture performed on

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September 2 revealed an opalescent fluid under 200 mm. of spinal fluid pressure, containing 80 erythrocytes and 5,900 white blood cells per cu. mm.; 92 per cent of the latter were polymorphonuclear cells and 8 per cent were mononuclears. The Pandy reaction was 4+. Direct smear showed no stainable microorganisms and a culture of the spinal fluid yielded no growth in 48 hours. The glucose content of the fluid was 61 mg., protein 69 mg., and chloride 772 mg., per 100 cc. The blood count revealed 4,610,000 red blood cells, 16,450 white blood cells per cu. mm., with 14 gm. of hemoglobin (90 per cent), and a differential white cell count of 89 per cent polymorphonuclears (79 per cent segmented, 10 per cent non-segmented), 9 per cent lymphocytes, and 2 per cent monocytes.

Culture of the blood drawn on September 1 later revealed growth of a coagulase positive hemolytic *Staphylococcus aureus*. This was interpreted as a possibly pathogenic organism, but the finding was not conclusive since this may occur in contamination.

It was first thought that a left-sided cerebral lesion with contiguous meningitis of infectious origin was present. After spinal puncture the patient was placed on sulfadiazine and Aureomycin.

On September 3 complete aphasia and spastic right hemiplegia had supervened; the neck was stiff and Brudzinski and Kernig signs were noted in the left extremities. The optic disks were normal. Otologic examination revealed no evidence of infection in the ears. The patient was placed on penicillin also and an indwelling catheter was inserted.

On September 4 the patient was worse. She was stuporous, and there was definite nuchal rigidity with positive Kernig and Brudzinski signs. The right side was less spastic but still paretic. The left leg was weak. The tendon reflexes on the left side were more brisk and there was patellar clonus on the left but not on the right. Bilateral Babinski and Hoffmann signs were present. The fundi and pupils appeared normal. There was right lower facial weakness. There seemed to be some impairment of ocular movements. The abdominal reflexes were absent. Spinal puncture revealed a turbid fluid under a pressure of 130 mm. of spinal fluid. No report of the cell count on this fluid could be found in the record entry. The patient continued to be stuporous and later that day rigidity of all extremities and a general appearance like that of decerebrate rigidity was noted. A blood culture taken on this day was subsequently found to be sterile.

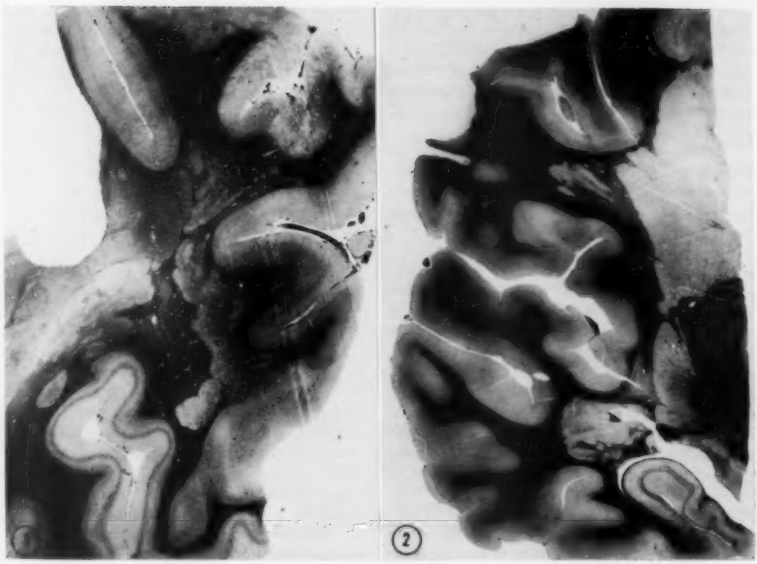
On September 5 the blood Kahn reaction was negative. Total serum proteins were 7.0 gm., serum albumin was 3.05 gm., and serum globulin was 3.95 gm., per 100 cc. Blood glucose was 142 mg. per 100 cc. Blood urea nitrogen was 17.4 mg., uric acid 2.6 mg., per 100 cc. Serologic tests for the common neurotropic virus diseases were negative. Stupor and Cheyne-Stokes respiration were noted. The reflexes in the upper extremities were very difficult to elicit. The arms were held in internal rotation with flexion at the wrists; the feet were in the equinovarus position.

On September 6 the patient delivered spontaneously a dead fetus with the placenta. The fetus was of a size compatible with 16 to 18 weeks gestation even though the pregnancy was estimated as 24 weeks in duration. Spinal fluid on this day was found to be clear and under normal pressure; there were no red blood cells, 232 white blood cells per cu. mm., with 32 per cent polymorphonuclear cells and 68 per cent mononuclear cells; the Pandy reaction was 2+. A subsequent report of a one week culture of the spinal fluid revealed no growth.

On September 7 it was necessary to do an emergency tracheotomy. On this day the left extremities were flaccid, with some resistance in the left upper arm and a closed position of the left hand. Bilateral extensor plantar responses were present.

On September 8 another spinal puncture revealed clear fluid under normal pressure (140 mm.). There were 12 red blood cells and 63 white blood cells (2 polymorphonuclears, 61 mononuclears). The Pandy reaction was reported as a trace. The patient's temperature continued to be slightly elevated (100 to 101° F., rectally). No skin eruption was found.

The patient's condition remained stationary except that on September 11 she seemed a little improved. Periodically her eyes turned and her neck became stiff. Flexion of the head brought her eyes down and loosened her neck. The spastic extension had disappeared from the four extremities. The knee jerks were present but hyperactive and the ankle jerks were absent. There were no pathologic reflexes. The disks were normal. The only spontaneous movements were occasional eye blinks. The rectal tem-



Figs. 1 and 2. Sclerosis through the cerebrum stained with Weil method, showing large areas of demyelination.

perature fluctuated between 101° and 103° F.

However, evidence of thrombocytopenic blood dycrasia appeared in the form of showers of petechiae, hematuria, and tarry stools. On September 13 the platelets numbered 103,600 per cu. mm. Respirations gradually became weaker and anuria developed. The patient died on September 16, less than 16 days after the onset of illness.

AUTOPSY

In addition to the cerebral findings, autopsy showed the following: acute hemorrhagic tracheobronchitis and acute bronchopneumonia of the right lung, with minimal pulmonary edema; severe acute ulcerative enterocolitis; edema of myocardium; bilateral hydrothorax and ascites; focal, acute capillary cholangiolitis; focal hemorrhages of spleen and urinary bladder; hyperplasia of acidophilic cells of hypophysis; cortical adenomas of the suprarenals; postpartum uterus.

The formalin-fixed brain revealed a foramen magnum pressure furrow and small herniations on either side of the tentorium cerebelli, more on the left. The leptomeninges were transparent. The surface blood vessels were engorged. The brainstem and cerebellum appeared macroscopically unaltered. There was extensive alteration of the subcortical white matter of both sides of the cerebrum. The centrum semiovale had a gelatinous appearance and texture from the frontal to the occipital poles, although the white matter immediately beneath the cortex seemed unchanged. A similar appearance was noted in the white matter of the temporal lobes. The right occipital lobe was the site of an area of fresh hemorrhagic necrosis, which occupied an area about a centimeter in diameter on the dorsolateral surface of the occipital cortex. Scattered through the white matter other than in the occipital lobe were minute petechial hemorrhages.

The microscopic studies were done on celloidin and paraffin embedded material stained by hematoxylin and eosin, thionin, and Weil methods. The silver stains for axis cylinders were not successful. The essential cytologic and vascular morphology (excepting that revealed by metallic impregnation methods) could be made out, but not

with sufficient clarity for good photographic reproductions. It is debatable whether this poor acceptance of stains represented some error or untoward effect of fixation and processing or instead reflected an antemortem necrotizing change, although the former explanation seems more probable.

Myelin sheath stains revealed large irregular areas of demyelination in the central white matter (figures 1 and 2), largely sparing the basal ganglia. The darker central portion of the large demyelinated area in figure 1 represents an area containing some undemyelinated fibers. Microscopic examination of the little spots of demyelination in the corpus callosum adjacent to the confluent area revealed these to be minute foci of softening crowded with gitter cells, often about a central vessel where some lymphocytes and plasma cells (brought out by hematoxylin and eosin technic) not uncommonly appeared among the gitter cells crowding the perivascular space. The main demyelinated area revealed increase in glial nuclei with some gemistocytic forms, fairly numerous gitter cells diffusely scattered and here and there concentrated as in frank softening, with perivascular accumulations of gitter cells. Some of these perivascular collections showed also a mixture of lymphocytes and plasma cells, especially near the periphery of the large demyelinated area shown in figure 1. The ventricular wall contained a perivascular monocytic infiltration surrounded for some distance by normal appearing brain substances. The brainstem, cerebellum, and basal ganglia in representative smaller sections revealed no demyelination, but there was marked hyperemia of the thalamus, adjacent internal capsule, rostral and caudal pons, and the medulla oblongata. In the section through Ammon's horn formation, the larger blood vessels in the ventricular wall appeared empty (in contrast to the dilated blood filled vessels in the hyperemic sites), and their dilated perivascular spaces contained numerous cells of the lymphocytic series, including plasma cells. In the meninges of the sections through the third ventricle and basal ganglia there were diffuse extravasations of erythrocytes, some proliferation of arachnoidal mesothelial cells and possibly connective tissue increase, and occasional multinuclear histiocytes.

One of the small sections of cerebral cortex and subcortex revealed no demyelination. In the leptomeninges there were small numbers of large mononuclears and very occasional polymorphonuclear cells, few scavenger cells containing hemosiderin in addition to infrequent multinuclear histocytes (as occur in the wake of recovery from purulent leptomeningitis). There was slight glial hyperplasia in the first cortical layer. The larger cortical ganglion cells were generally well preserved except for swelling and eccentric nuclear placement in a small minority of the cells seen. Infiltrative inflammatory reaction was lacking in the cortex; the subcortex showed merely small accumulations of attenuated scavenger cells in the perivascular spaces.

Another cortical section was through the area of hemorrhagic transformation in the right occipital lobe. This revealed multiple hemorrhages (chiefly capillary, or from coalescence of such hemorrhages) with a seminecrotic appearance of intervening brain tissue, and adjacent to areas of most intense hemorrhagic change, the picture of early anemic softening (gitter cell formation with many of these still in situ, necrotic appearance of parenchyma, and capillary sprouting). Cellular infiltration with polymorphonuclears as often occurs in early softening, or perivascular mononuclear infiltration of the cortex, and significant cellular reaction in the leptomeninges were lacking.

Other cortical sections revealed demyelination either subcortically or actually extending into the cortex. Some of the demyelinated zones had a spongy appearance, showing glial strands coursing longitudinally between holes in the ground substance and fairly numerous gemistocytic astrocytes. The perivascular (or adventitial) spaces about many of the venules were distended with compound granular corpuscles, and the latter could be seen scattered in the tissue interstices. Capillary sprouting was prominent in some areas. The endothelium of the small vessels appeared swollen. A number of small vessels showed infiltration not only with gitter cells, but also with lymphocytes and plasma cells. The normally myelinated cortex showed no significant inflammatory changes.

In some sections the cortical ganglion cells showed considerable staining alteration, with marked chromatolysis and even the picture of so-called severe ganglion cell disease, without any accompanying cellular infiltrations. The leptomeninges were relatively clear. Another cortical section presenting subcortical demyelination, gliosis, and incomplete softening revealed marked congestion of the surface leptomeninges which contained extravasated red blood cells

and occasional polymorphonuclear leukocytes and multinuclear histiocytes.

Still another section through cortex of unidentified situation showed a wedge of demyelination and gliosis in the subcortex, apparently the periphery of a larger confluent demyelinized zone. Besides loosely scattered gitter cells in the tissue and proliferated astroglial cells, in places polymorphonuclear leukocytes were loosely strewn through the tissue. The regional perivascular spaces contained varying types of infiltrates but some of these were predominantly polymorphonuclear, with a sprinkling of brown pigment-containing scavenger cells, only few ordinary gitter cells, and an occasional round cell. Some of these infiltrates were up to ten cells deep. Other perivascular infiltrates in the subcortex contained plasma cells, polymorphonuclear leukocytes, and lymphocytes in equal numbers with only occasional gitter cells.

DISCUSSION

The lesions in the brain were like those described in the more acute cases of diffuse sclerosis, except for not insignificant inflammatory reaction within demyelinated and partially softened areas and the presence of a focus of hemorrhagic softening (secondary to the blood dyscrasia?).

However, certain clinical features of this case would seem to be incompatible with diffuse sclerosis alone, whatever that heterogenous clinical entity may be. In no reported and well documented case of diffuse sclerosis has there been found pleocytosis of a magnitude of thousands of cells. Pleocytosis in diffuse sclerosis has occasionally been noted, as in the case of Winkelman and Moore,[1] with 623 cells per cu. mm., chiefly lymphocytes. No organisms were found on smear or culture of the fluid, but it is not inconceivable that inability to find them was a laboratory failing and that perhaps the patient suffered from purulent bacterial meningitis which responded to treatment with penicillin and sulfadiazine. There were clinical signs of meningeal irritation, which gave the impression that there seemed to be primary brain disease with secondary involvement of the meninges. One blood culture before chemotherapy was begun indicated the presence of a staphylococcic bacteremia of a possibly pathogenic nature. Fever and leukocytosis were further evidence of some infectious process, although there is a "physiologic leukocytosis of pregnancy." However, negative results of culture of spinal fluid obtained from an acute case of presumed staphylococcic meningitis before institution of chemotherapy would seem significant.

The duration of this illness was shorter than that of any of the 50 cases of diffuse sclerosis in adolescents or adults compiled by Bouman,[2] except for one of nine days' duration described by Stewart, Greenfield, and Blandy.[3] This case was marked by scattered small foci of demyelination but not by the large lesions demonstrated here, and the clinical course was more typical for diffuse sclerosis (beginning in an afebrile manner with rapidly developing blindness and stupor, associated with a normal spinal fluid).

Scheinker[4] has reported on leukoencephalitis associated with purulent leptomeningitis, but the appearances in his cases were quite different from those in our case, there being small disseminated focal areas of demyelination in the subcortical white matter chiefly in the vicinity of thrombosed veins, with features of disseminated purulent leukoencephalitis. His patients lived only a few days and florid purulent meningitis was present. In this case the large confluent lesions in the white matter in many regions are like those in diffuse sclerosis and seem quite different from the appearances in Scheinker's cases, but this patient survived longer and did show subcortical polymorphonuclear perivascular infiltrations in places. Any resemblance of this case to Scheinker's observations must be predicated on the assumption that a purulent leptomeningitis had existed and

had been cured by sulfonamide and antibiotic therapy, but that a toxic or neuro-allergic myelinolytic process had continued to be operative, resulting in coalescence of numerous initially small, perivascular foci of demyelination.

In any event the whole clinical picture suggested some infectious process — sudden onset of a confusional state associated with fever, meningeal signs, marked pleocytosis, leukocytosis and possibly bacteremia, and associated with acute ulcerative enterocolitis (although this enterocolitis was interpreted by the pathologist as one of the terminal events or one of the immediate causes of death). Antibiotic therapy may have modified the natural course of a bacterial infection localizing in the leptomeninges, but bacterial meningitis has not been known to cause extensive subcortical demyelination and softening. It might be speculated that a pathologic appearance consistent with diffuse sclerosis was rapidly caused in some way as a neuro-allergic reaction to bacteremia and bacterial meningitis; or that the former disease, by the most unbelievable of coincidences was developing independently of, and simultaneously with, a meningitis that responded to chemotherapy; or finally that this case was one of acute diffuse sclerosis with aseptic(?) meningeal reaction secondary to rapid demyelination.

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The minor attacks of epilepsy vary much in character, and hence patients speak of them under various designations, such as "sensations," "faints," "losses," "turns," "giddiness," and, in America, "spells." Hence also their epileptic nature, and their connection with severer attacks, are often not known to the patients or their friends. It is not always easy to ascertain their exact character on account of their very short duration. Their onset may or may not be attended by any sensation of which the patient is conscious, and when it is not so attended, the difficulty of ascertaining their character is increased. In the majority of cases the patient is unconscious during the attack, but in a few instances consciousness is retained, although it is probably always modified in some degree.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

NEWSLETTER

AUGUST, 1954

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AMERICAN ACADEMY OF NEUROLOGY

ANA Meets In Atlantic City The seventy-ninth annual meeting of the American Neurological Association was held at the Hotel Claridge, Atlantic City (June 14-16).... Following tradition, the scientific program was opened with the presidential address by Roland P. Mackay, followed by a wide range of carefully selected 10 minute papers in both basic and clinical neurology. A special evening session was set aside (June 14) for longer presentations, using motion pictures and other forms of visual aids. Highlighted on the evening program was a presentation by Prof. G. H. Monrad-Krohn of Oslo, Norway.... The presentation of papers was implemented by a display of scientific exhibits on such timely subjects as tissue culture; newer neurosurgical approaches; metabolism of the epileptogenic cortex in man; ionic exchanges in neuromuscular disorders; and anatomic studies in frontal leukotomy.... On Tuesday evening (June 15), there was the usual pause in scientific activity for the Association's annual dinner.... Also, luncheon meetings were held for the medical advisory boards of the Muscular Dystrophy Associations and the Myasthenia Gravis Foundation.... The ANA convention was preceded by the eighth annual meeting of the American Electroencephalographic Society (June 11-13) and the thirtieth meeting of the American Association of Neuropathologists.... In 1955 the ANA will convene in Chicago.

Toward a Neurology Of Behavior In his ANA presidential address, Roland P. Mackay called for a neurology of behavior as the ultimate challenge for neurologists. He maintains that the goals of neurology must transcend the elucidation of disease to a clarification of the total homeostatic adjustment of the organism. Thus, he believes "the nervous system is the organ of the mind, no matter what view one may take as to the nature of mind".... Dr. Mackay traced the development of our present knowledge of the neurology of behavior from the early work on the cerebral cortex in the nineteenth century to more modern findings, such as those on the "visceral brain" and the reticular activating system; but pointed out that these and other achievements, while impressive, are still far from formulating a neurologic theory of behavior. "What we need most of all," Dr. Mackay stated, "is a method of studying the nervous system as a whole and in its several parts during normal behavior."

While praising as promising the introduction of newer methodologies such as Lilly's simultaneous electrical recordings from numerous adjacent cortical points, he stated that "they scarcely satisfy our great need for insight into the neurologic basis for behavior."... Hence, Dr. Mackay in his paper, directs us to classical psychology with the aim of finding underlying neurologic counterparts for what, in psychology, is called concept and character. Briefly paraphrasing Dr. Mackay's reasoning, the neurologic representation of the psychological concept consists of a specific sensitivity of a neuronal network to spatiotemporal patterns of incoming sensory impulses. For these dynamic patterns of receptive sensitivity, Mackay suggests the term esthesotype. Pursuing further his thesis for a neurology of behavior, he defines motor memories in aggregate as constituting the neurologic counterpart of character. To motor memory he has applied the term kinemnesis, which he considers a generalized abstraction of innumerable specific acts, just as the esthesotype applies to generalized, patterned clusters of afferent stimuli. Character, therefore, is the aggregate of one's kinemnesis, which is the motor homologue of the sensory concept (or its underlying esthesotype).... In summary, Mackay postulates "the most intriguing problem of all is to discover the mechanisms of neuronal patterns of sensitivity and response in neural networks, and specifically how the patterns are established, reinforced, and modified by the experiences and activities of life," and concludes that "only a consideration of the nervous system as a whole can solve these problems and lead to a neurology of behavior".... The full text of Dr. Mackay's paper is to be published.

Forster Elected Chairman Of Joint Committee Francis M. Forster was elected chairman of the newly established joint committee of the American Neurological Association and the American Academy of Neurology on survey of neurologic education, at the annual meeting of the ANA (June 15). Other members of the committee are: Bernard J. Alpers, A. L. Sahs, and Pearce Bailey, representing the ANA; Dr. Forster, A. B. Baker, and A. S. Rose, representing the AAN. Preliminary plans of the committee were formulated and a second session will be held at the time of the New York meeting in December.

New ANA Officers And Representatives The new officers of the ANA are: president, Percival Bailey; president-elect, J. M. Nielsen; first vice-president, A. R. Vonderahe; and second vice-president, Paul C. Bucy. H. Houston Merritt and Charles Rupp continue as secretary-treasurer and assistant secretary, respectively.... Appointed as representatives of the ANA to the American Board of Psychiatry and Neurology were Knox Finley (1954-1957) and Paul I. Yakovlev (1954-1958). Edgar A.

Kahn was appointed representative of the ANA to the American Board of Neurological Surgery.... New ANA members elected at the meeting are: William K. Jordan, Clark H. Millikan, Morton Nathanson, Milton Tarlau, Melvin D. Yahr. Elected as associate members were Leslie Freeman and Jerzy E. Rose.... Following council recommendation, Henry W. Woltman, Frederick P. Moersch, Henry R. Viets, and William P. Van Wagenen were elected to senior membership.

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New Deadlines For NINDB Grants and Stipends The fiscal year 1955 (July 1, 1954 to June 30, 1955) deadline for the receipt of research grant applications to the National Institute of Neurological Diseases and Blindness are November 1, 1954, March 1, and July 1, 1955. The deadline for graduate medical training grants is November 1, 1954.... Applications for stipends for research fellowships or (clinical) traineeships (awards to physicians and other post-doctoral candidates who desire specialized training in neurologic or sensory disorders or rehabilitation), will be accepted at any time. Processing, review, and approval of these applications require from 60 to 90 days.... Application forms and additional information about these programs may be obtained from Chief, Extramural Programs, National Institute of Neurological Diseases and Blindness, Bethesda 14, Maryland.

Congress Increases NINDB Appropriation The Congress increased the fiscal year 1955 appropriation of the National Institute of Neurological Diseases and Blindness from $4,500,000 to $7,600,500. This provides for an increase of $1,200,000 for research grant awards and an increase of a half million dollars for graduate training grant awards.... The training grant awards are made to institutions to initiate, expand, or improve graduate medical training programs in neurologic and ophthalmic disorders. Their primary purpose is to increase the number of clinical teachers and clinical researchers who wish to pursue academic careers in these fields.

New Diplomates In Neurology As a result of the last examinations of the American Board of Psychiatry and Neurology, held in Chicago (May 10-11), nine physicians were certified in neurology. The new diplomates are: Ian A. Brown, University of Minnesota, Minneapolis; Maurice P. Carlin, 912 S. Wood St., Chicago; David Barrett Clark, 601 N. Broadway, Baltimore, Md.; Philip Rogers Dodge, U. S. Army Hospital, Fort Campbell, Ky.; Robert Allen Fishman, Neurological Institute, New York City; John M. Harter, 450 Sutter Street, San Francisco (supplementary certification); Lewis L. Levy, Louisville General Hospital, Louisville, Ky.; Israel H. Schuleman,

127 12th St., Galveston, Tex.; John W. Schut, Galesburg State Research Hospital, Galesburg, Ill.; Edward F. Vastola, Rural Route #10, Box 527A, Ferguson, Mo..... Present president of the board is Kenneth E. Appel; the secretary-treasurer, to whom all communications should be sent, is David A. Boyd, Jr., Mayo Clinic, Rochester, Minn.

Schreiber Becomes President-Elect Of Harvey Cushing Society At the twenty-second annual meeting of the Harvey Cushing Society, held in Santa Fe (May 6-8), Frederic Schreiber of Detroit was elected president-elect; Richard U. Light, vice-president; David L. Reeves continues as secretary-treasurer, while Edgar Kahn was elected member of the executive committee. President of the society for 1954-1955 is Harry Wilkins of Oklahoma City.

AMA Section Elects New Officers At the annual meeting of the Section on Nervous and Mental Diseases of the American Medical Association in San Francisco, June 23, Francis J. Braceland was elected chairman and Joseph P. Evans, vice chairman. Karl O. Von Hagen continues as secretary, Hans H. Reese as delegate, and G. Wilse Robinson as representative to Scientific Exhibit.

Here and There H. Houston Merritt and Roland P. Mackay have been appointed to the Editorial Board of Neurology.... Russell N. DeJong, editor-in-chief, has left for a visit to the National Hospital, Queen Square, London, and Mabel G. Masten, newly appointed associate editor, will act during his absence... J. G. Greenfield of London is coming to NINDB as a visiting scientist in neuropathology.... New certificates of membership in the Academy are now available for a fee of $3.00.... The 1954 president of the French Neurological Society (Societe Francaise de Neurologie) is Dr. M. A. Thevenard, who succeeds Dr. M. R. Moreau.... Dr. Michael Kremer has succeeded Dr. Macdonald Critchley as Dean of the Institute of Neurology, National Hospital, Queen Square, London.... The fifth Symposium on Vegetative Neurology will be held at the Palais Auersperg in Vienna, Austria, August 31 to Sept. 1, 1954. The subject of the symposium is the Physiology and Pathology of Temperature Regulation. Included in the program from the United States are Webb Haymaker (Pathology of Heat Stroke) and Robert B. Lewis (Pathogenesis of Local Cold Injury). All inquiries concerning travel and accommodations should be directed to Dr. W. Schwabl, Secretary of the Symposium, Springer-Verlag, Vienna I, Molkerbastei 5.

Percy Bailey

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HYDROCORTONE BY SHARP AND DOHME

'Hydrocortone' lotion, containing hydrocortone 1 per cent, packaged in a plastic squeeze-type bottle for ease of application in topical therapy, has been released by Sharp & Dohme, Philadelphia Division of Merck & Co., Inc. This form of 'Hydrocortone' for topical use resulted from research and clinical studies directed toward developing a dosage from more cosmetically acceptable, simpler to apply, more effective because of its spreading qualities, and more advantageous when large areas are involved.. A further factor was ease of application to various dermatoses of the hairy areas.

Clinical investigations, according to the announcement, have revealed a high degree of patient acceptance. Reports indicate that the lotion does not burn or sting when applied; does not stain skin, clothing or other objects; has no disagreeable odor; and is not uncomfortable or unsightly when rubbed in well. There were no instances of allergic sensitization even after prolonged use, and no evidence of absorption with resulting systemic affects.

STUDIES SHOW NEW AMEBICIDE HIGHLY-ACTIVE IN SMALL DOSE

Mantomide, a new amebicidal drug, has been found to be more highly active in considerably smaller doses against Endamoeba histolytica than certain broad-spectrum antibiotics and other commonly used drugs in chronic intestinal amebiasis. The tests further demonstrated that the drug is "essentially nontoxic" in human patients as well as in laboratory animals. Containing neither iodine nor arsenic, chemically it is N-(2, 4-dichlorobenzyl)-N-(2-hydroxyethyl) dichloroacetamide.

Mantomide was synthesized at the Sterling-Winthrop Research Institute. Findings of two separate studies are reported. In one study, twenty-four patients with chronic amebiasis were treated with Mantomide and kept under observation for a minimum of six weeks. The dose was calculated according to the patient's age: to those less than five years, 250 mg. were given three times daily for eight days; 500 mg. were given three times daily for 10 days to patients between five and ten years; and 750 mg. to 1.0 gram were given three times a day for 10 and eight days, respectively, to those over 10 years.

The parasites were eliminated in all 24 cases and smear tests were found negative six to 28 weeks later.

In the second study the drug's high amebicidal activity and low toxicity was demonstrated in tests with animals and in human patients at the Sterling-Winthrop Research Institute. Observing that Mantomide did not affect bacteria normally found in the intestines, the investigations report that the activity against E. histolytica "is presumed to be direct."

"CONQUERORS OF YELLOW FEVER" PRESENTED TO ARMY MEDICAL GRADUATE SCHOOL BY WYETH LABORATORIES

"Conquerors of Yellow Fever," a painting of one of the great moments in medical history from among the Wyeth Laboratories collection, "Pioneers of American Medicine," was presented to the Army Medical Service Graduate School in Washington recently. Dr. George E. Farrar, Jr., medical director of Wyeth Laboratories, made the presentation at a ceremony in the Walter Reed Army Medical School. Colonel William S. Stone, USA (MC), commandant of the school, accepted the painting for the Center. Dr. Farrar expressed the hope that the painting "may help continue to build the pioneer spirit among the Army Medical Corps which the event in the painting symbolizes."

(Continued on page 16A)

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(Continued from page 15A)

Dr. Farrar went on to say that Wyeth Laboratories recognized many years ago that the citizens of our country knew little if anything concerning contributions to the health and welfare of our nation made by their own physicians. "In order to pay proper and fitting tribute to those doctors who labored in anonymity, but whose work was of singular importance, Wyeth proposed to execute a series of paintings which would recapture great moments in U. S. medical history," he said. The series was painted by the distinguished illustrator and muralist, Dean Cornwell, N. A. A panel of physicians selected the important moments in American medical history for recreation. Months of investigation and research went into preliminary work on each painting.

With Major Walter Reed and Dr. Carlos Finlay looking on, the painting shows Dr. Lazear, who died a month later as a result of self-experimentation, inoculating Dr. Carroll with an infected mosquito. The event occured on the grounds of Columbia Barracks Post Hospital of the United States Army in Cuba August 6, 1900. This experiment indicated that the mosquito was the carrier of yellow fever.

AYERST RELEASES "CLUSINTRIN"

Presented as the most practical and up-to-date approach in the treatment of anemias, "Clusintrin," a preparation providing U.S.P. standardized B_{12} with intrinsic factor concentrate, additional B_{12}, iron, and a full complement of hemopoietic elements as contained in Spies' basic formula, has just been released by Ayerst Laboratories, Rouse's Point, N. Y.

Each "Clusintrin" capsule provides: Vitamin B_{12} with intrinsic factor concentrate, 0.33 U.S.P. Units; Vitamin B_{12} U.S.P. (crystalline), 25.0 mcg.; Folic acid U.S.P., 1.67 mg.; Vitamin C (ascorbic acid), 50. mg.; Thiamine mononitrate (B_1), 3.34 mg.; Riboflavin (B_2), 3.34 mg.; Nicotinamide, 50.0 mg.; Ferrous sulfate exsic., 200.0 mg. "Clusintrin" is available in bottles of 100 and 1,000 capsules.

NEW BLOCKING AGENT

Ilidar, a new adrenolytic blocking agent for use in the treatment of vasospasm, has just been introduced by Hoffmann-La Roche Inc. of Nutley, New Jersey. This compound, a dibenzazepine derivative, is particularly useful in the symptomatic relief of circulatory conditions characterized by aching, coldness, tingling and numbness of the extremities. Ilidar 'Roche' has a fourfold therapeutic effect in vasospasm. It causes dilation of the peripheral blood vessels by sympatholytic and adrenolytic action, by epinephrine reversal and by direct vasodilation. Ilidar Phosphate is available in coated oral tablets, 25 mg each, bottles of 100 and 500.

ABBOTT'S NEW ERYTHROCIN LACTOBIONATE

This is a new soluble salt of Erythrocin for intravenous or intramuscular injection in the treatment of patients who cannot take oral medication or in whom immediate high Erythrocin blood levels are important. Should be supplanted by oral medication when practicable. It is indicated in the treatment of serious infections caused by staphylococci, streptococci and pneumococci and especially indicated in infections produced by strains of those organisms which are resistant to other antibiotics—or when the patient is allergic to penicillin and other antibiotics. The makers are Abbott Laboratories, North Chicago, Ill.

DRUG FOR SIMPLE, ACCURATE PREGNANCY TESTS MADE AVAILARLE BY WARNER-CHILCOTT LABORATORIES

A drug which induces menstruation now makes possible a simple and accurate test for pregnancy when used under certain conditions. Called Stigmonene Bromide, the agent was found to be effective in three separate studies involving more than 250 selected patients.

The test is based on the ability of the drug to induce menstruation that has been delayed for reasons other than pregnancy or organic disturbances. The studies showed that, if menstruation is not brought about by injections of the drug, the women can be considered pregnant.

The Stigmonene Bromide pregnancy test proved completely reliable in 77 women with simple delayed menstruation at St. Vincent's Hospital, New York City, according to a report by Drs. Thomas E. Lavell, George Knauer, Jr., and C. McNeil Winterhalter.

Stigmonene Bromide is being made available by Warner-Chilcott Laboratories, New York City, the pharmaceutical division of Warner-Hudnut, Inc. According to Dr. George Mangun, Warner-Chilcott director of research, "Stigmonene Bromide offers a safe, simple and accurate pregnancy test, in the absence of organic disturbances, without need of complicated laboratory analysis. In addition it provides an important aid in the treatment of simple delayed menstruation."

Stigmonene Bromide inhibits the action of cholinesterase, a body chemical which acts to prevent the transmission of nerve impulses involved in normal menstruation.

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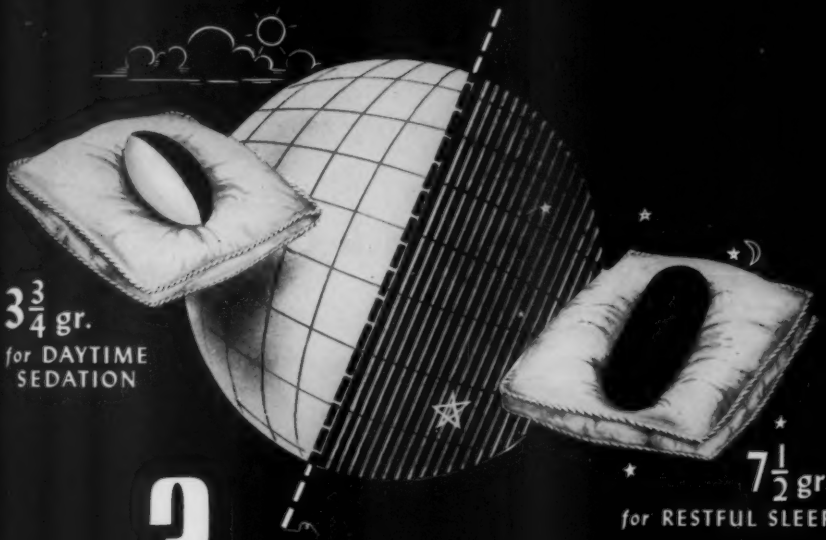

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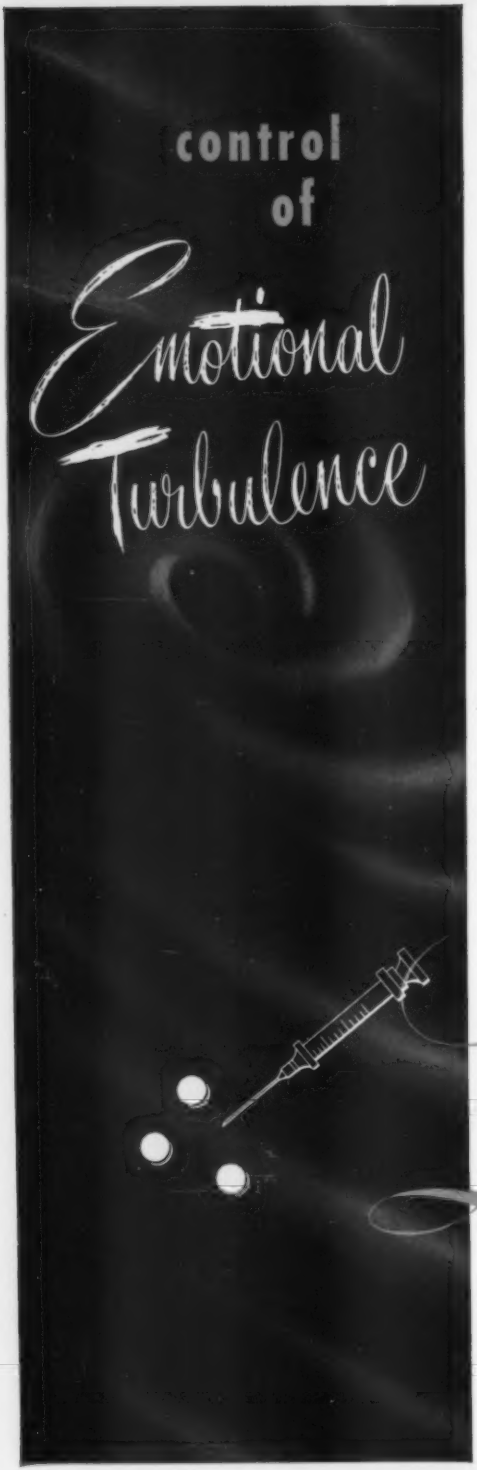

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